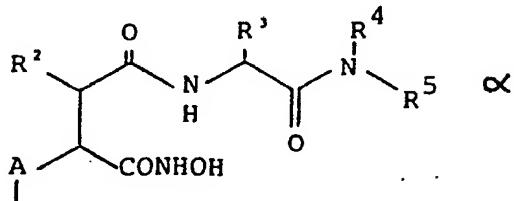
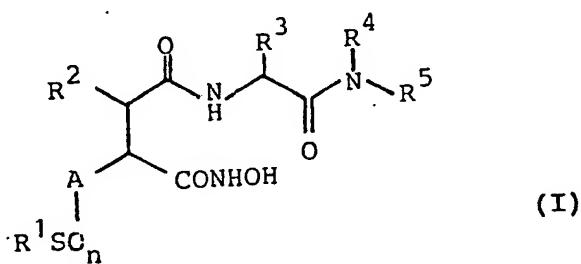




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |    |                                                                                                                                                                                                                                                                                                                                                                                                               |
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| (54) Title: HYDROXAMIC ACID BASED COLLAGENASE INHIBITORS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |    |                                                                                                                                                                                                                                                                                                                                                                                                               |



## (57) Abstract

Compounds of general formula (I), wherein R<sup>1</sup> represents hydrogen or an alkyl, phenyl, thiophenyl, substituted phenyl, phenylalkyl, heterocycl, alkylcarbonyl phenacyl or substituted phenacyl group; or, when n = 0, R<sup>1</sup> represents SR<sup>X</sup>, wherein RX represents a group ( $\alpha$ ); R<sup>2</sup> represents a hydrogen atom or an alkyl, alkenyl, phenylalkyl, cycloalkylalkyl or cycloalkenylalkyl group; R<sup>3</sup> represents an amino acid residue with R or S stereochemistry or an alkyl, benzyl, (C<sub>1</sub>-C<sub>6</sub> alkoxy) benzyl or benzyloxy(C<sub>1</sub>-C<sub>6</sub> alkyl) group; R<sup>4</sup> represents a hydrogen atom or an alkyl group; R<sup>5</sup> represents a hydrogen atom or a methyl group; n is an integer having the value 0, 1 or 2; and A represents a hydrocarbon chain optionally substituted with one or more alkyl, phenyl or substituted phenyl groups; and their salts and N-oxides are collagenase inhibitors and are useful in the management of disease involving tissue degradation and/or the promotion of wound healing. Diseases involving tissue degradation include arthropathy (particularly rheumatoid arthritis), inflammation, dermatological diseases, bone resorption diseases and tumour invasion.

Atty. Docket No. 01136/1/US

Serial No. 10/603,441

Daniel P. Becker, et al.

Reference 47 of 67

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1                   HYDROXAMIC ACID BASED COLLAGENASE INHIBITORS.  
2

3     This invention relates to pharmaceutically and  
4     veterinarily active compounds, which are derivatives of  
5     hydroxamic acid.

6

7     The compounds of the present invention act as  
8     inhibitors of metalloproteases involved in tissue  
9     degradation, such as collagenase, which initiates  
10    collagen breakdown, stromelysin (protoglycanase),  
11    gelatinase and collagenase (IV). There is evidence  
12    implicating collagenase as one of the key enzymes in  
13    the breakdown of articular cartilage and bone in  
14    rheumatoid arthritis (Arthritis and Rheumatism, 20,  
15    1231 - 1239, 1977). Potent inhibitors of collagenase  
16    and other metalloproteases involved in tissue  
17    degradation are useful in the treatment of rheumatoid  
18    arthritis and related diseases in which collagenolytic  
19    activity is important. Inhibitors of metalloproteases  
20    of this type can therefore be used in treating or  
21    preventing conditions which involve tissue breakdown;  
22    they are therefore useful in the treatment of  
23    arthropathy, dermatological conditions, bone  
24    resorption, inflammatory diseases and tumour invasion  
25    and in the promotion of wound healing. Specifically,  
26    compounds of the present invention may be useful in the  
27    treatment of osteopenias such as osteoporosis,  
28    rheumatoid arthritis, osteoarthritis, periodontitis,  
29    gingivitis, corneal ulceration and tumour invasion.

30

31    A number of small peptide like compounds wh:  
32    inhibit metalloproteases have been described. Pe  
33    the most notable of these are those relating

1 angiotensin converting enzyme (ACE) where such  
2 agents act to block the conversion of the decapeptide  
3 angiotensin I to angiotensin II a potent pressor  
4 substance. Compounds of this type are described in  
5 EP-A-0012401.

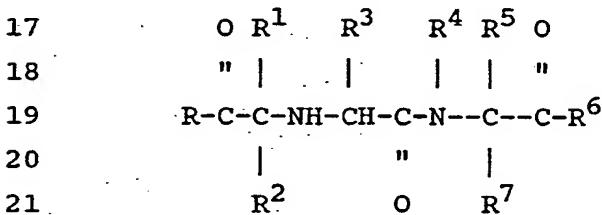
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7 Certain hydroxamic acids have been suggested as  
8 collagenase inhibitors as in US-A-4599361 and  
9 EP-A-0236872. Other hydroxamic acids have been prepared  
10 as ACE inhibitors, for example in US-A-4105789, while  
11 still others have been described as enkephalinase  
12 inhibitors as in US-A-4496540.

13

14 EP-A-0012401 discloses antihypertensive compounds of  
15 the formula:

16



22

23 wherein

24

25 R and R<sup>6</sup> are the same or different and are hydroxy,  
26 alkoxy, alkenoxy, dialkylamino alkoxy, acylamino  
27 alkoxy, acyloxy alkoxy, aryloxy, alkyloxy, substituted  
28 aryloxy or substituted aralkoxy wherein the substituent  
29 is methyl, halo, or methoxy, amino, alkylamino,  
30 dialkylamino, aralkylamino or hydroxyamino;

31

32

33

1 R<sup>1</sup> is hydrogen, alkyl of from 1 to 20 carbon atoms,  
2 including branched, cyclic and unsaturated alkyl  
3 groups;

4  
5 substituted alkyl wherein the substituent is halo,  
6 hydroxy, alkoxy, aryloxy amino, alkylamino,  
7 dialkylamino, acrylamino, arylamino, guanidino,  
8 imidazolyl, indolyl, mercapto, alkylthio, arylthio,  
9 carboxy, carboxamido, carbalkoxy, phenyl, substituted  
10 phenyl wherein the substituent is alkyl, alkoxy or  
11 halo; aralkyl or heteroaralkyl, aralkenyl or  
12 heteroaralkenyl, substituted aralkyl, substituted  
13 heteroaralkyl, substituted aralkenyl or substituted  
14 heteroaralkenyl, wherein the substituent is halor or  
15 dihalo, alkyl, hydroxy, alkoxy, amino, aminomethyl,  
16 acrylamino, dialkylamino, alkylamino, carboxyl,  
17 haloalkyl, cyano or sulphonamido, aralkyl or  
18 heteroaralkyl substituted on the alkyl portion by  
19 amino or acylamino;

20  
21 R<sup>2</sup> and R<sup>7</sup> are hydrogen or alkyl;

23 R<sup>3</sup> is hydrogen, alkyl, phenylalkyl,  
24 aminomethylphenylalkyl, hydroxyphenylalkyl,  
25 hydroxylalkyl, acetylaminoalkyl, acylaminoalkyl,  
26 acylaminoalkyl aminoalkyl, dimethylaminoalkyl,  
27 haloalkyl, guanidinoalkyl, imidazolylalkyl,  
28 indolylalkyl, mercaptoalkyl and alkylthioalkyl;

30 R<sup>4</sup> is hydrogen or alkyl;

1 R<sup>5</sup> is hydrogen, alkyl, phenyl, phenylalkyl,  
2 hydroxyphenylalkyl, hydroxyalkyl, aminoalkyl,  
3 guanidinoalkyl, imidazolylalkyl, indolylalkyl,  
4 mercaptoalkyl or alkylthioalkyl;

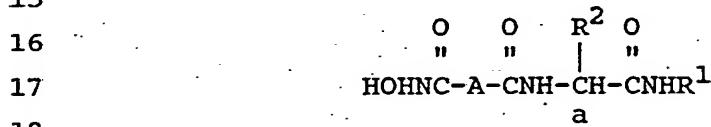
5

6 R<sup>4</sup> and R<sup>5</sup> may be connected together to form an alkylene  
7 bridge of from 2 to 4 carbon atoms, an alkylene bridge  
8 of from 2 to 3 carbon atoms and one sulphur atom, an  
9 alkylene bridge of from 3 to 4 carbon atoms containing  
10 a double bond or an alkylene bridge as above,  
11 substituted with hydroxy, alkoxy or alkyl and the  
12 pharmaceutically acceptable salts thereof.

13

14 US-A-4599361 discloses compounds of the formula:

15



18

19 wherein

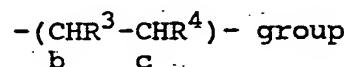
20 R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl;

21 R<sup>2</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl, benzyloxybenzyl, (C<sub>1</sub>-C<sub>6</sub>  
22 alkoxy)benzyl or benzyloxy(C<sub>1</sub>-C<sub>6</sub> alkyl);

23 a is a chiral centre with optional R or S  
24 stereochemistry;

25 A is a

26



28

29 or a -(CR<sup>3</sup>=CR<sup>4</sup>)- group wherein b and c are chiral  
30 centres with optional R or S stereochemistry;

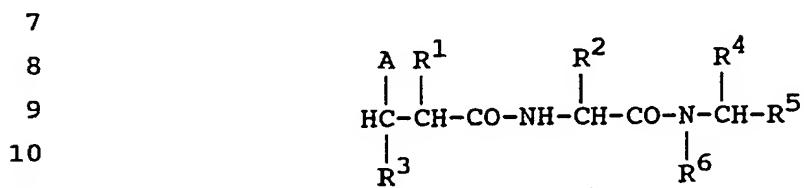
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32

33

1 R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl or phenyl(C<sub>1</sub>-C<sub>6</sub>  
2 alkyl) and R<sup>4</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl(C<sub>1</sub>-C<sub>6</sub>  
3 alkyl), cycloalkyl or cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkyl).

4  
5 EP-A-0236872 discloses generically compounds of the  
6 formula



13 wherein

14

15 A represents a group of the formula HN(OH)-CO- or  
16 HCO-N(OH)-;

17

18 R<sup>1</sup> represents a C<sub>2</sub>-C<sub>5</sub> alkyl group;

19

20 R<sup>2</sup> represents the characterising group of a natural  
21 alpha-amino acid in which the functional group can be  
22 protected, amino groups may be acylated and carboxyl  
23 groups can be amidated, with the proviso that R<sup>2</sup> can  
24 not represent hydrogen or a methyl group;

25

26 R<sup>3</sup> represents hydrogen or an amino, hydroxy, mercapto,  
27 C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> acylamino,  
28 C<sub>1</sub>-C<sub>6</sub>-alkylthio, aryl-(C<sub>1</sub>-C<sub>6</sub> alkyl)-,  
29 amino-(C<sub>1</sub>-C<sub>6</sub>-alkyl)-, hydroxy(C<sub>1</sub>-C<sub>6</sub>-alkyl)-,  
30 mercapto(C<sub>1</sub>-C<sub>6</sub> alkyl) or carboxy(C<sub>1</sub>-C<sub>6</sub> alkyl) group,

31

32

33

1 wherein the amino, hydroxy, mercapto or carboxyl groups  
2 can be protected and the amino groups may be acylated  
3 or the carboxyl groups may be amidated;

4 R<sup>4</sup> represents hydrogen or a methyl group;  
5

6 R<sup>5</sup> represents hydrogen or a C<sub>1</sub>-C<sub>6</sub> acyl, C<sub>1</sub>-C<sub>6</sub> alkoxy-  
7 C<sub>1</sub>-C<sub>6</sub> alkyl, di(C<sub>1</sub>-C<sub>6</sub>-alkoxy)methylene, carboxy, (C<sub>1</sub>-C<sub>6</sub>  
8 alkyl)carbiny, (C<sub>1</sub>-C<sub>6</sub> alkoxy)carbiny, arylmethoxy  
9 carbiny, (C<sub>1</sub>-C<sub>6</sub> alkyl)amino carbiny or arylamino  
10 carbiny group; and

11 R<sup>6</sup> represents hydroxy or a methylene group; or

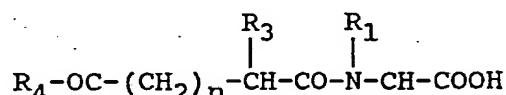
12 R<sup>2</sup> and R<sup>4</sup> together represent a group-(CH<sub>2</sub>)<sub>n</sub>-, wherein n  
13 represents a number from 4 to 11; or

14 R<sup>4</sup> and R<sup>5</sup> together represent a trimethylene group;

15 and pharmaceutically acceptable salts of such  
16 compounds, which are acid or basic.

17 US-A-4105789 generically discloses compounds which have  
18 the general formula

19



21

22 and salts thereof, wherein

23

24 R<sub>1</sub> is hydrogen, lower alkyl, phenyl lower alkylene,  
25 hydroxy-lower alkylene, hydroxyphenyl lower  
26 alkylene, amino-lower alkylene, guanidine lower

1       alkylene, mercapto-lower alkylene, lower  
2       alkyl-mercaptop-lower alkylene, imidazolyl lower  
3       alkylene, indolyl-lower alkylene or carbamoyl  
4       lower alkylene;  
5       R<sub>2</sub> is hydrogen or lower alkyl;  
6       R<sub>3</sub> is lower alkyl or phenyl lower alkylene;  
7       R<sub>4</sub> is hydroxy, lower alkoxy or hydroxyamino; and  
8       n is 1 or 2.

9  
10      US-A-4496540 discloses compounds of the general  
11      formula:

12

13           A-B-NHOH

14

15      wherein A is one of the aromatic group-containing amino  
16      acid residues L-tryptophyl, D-tryptophyl, L-tyrosyl,  
17      D-tyrosyl, L-phenylalanyl, or D-phenylalanyl, and B is  
18      one of the amino acids glycine, L-alanine, D-alanine,  
19      L-leucine, D-leucine, L-isoleucine, or D-isoleucine;  
20      and pharmaceutically acceptable salts thereof.

21

22      It would however be desirable to improve on the  
23      solubility of known collagenase inhibitors and/or  
24      stomelysin inhibitors (whether as the free base or the  
25      salt) and, furthermore, increases in activity have also  
26      been sought. It is not a simple matter, however, to  
27      predict what variations in known compounds would be  
28      desirable to increase or even retain activity; certain  
29      modifications of known hydroxamic acid derivatives have  
30      been found to lead to loss of activity.

31

32      According to a first aspect of the invention, there is  
33      provided a compound of general formula I:

1

2

3

4

5

6

7

8 wherein:

9

10 R<sup>1</sup> represents a C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, thiophenyl,  
 11 substituted phenyl, phenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 12 heterocyclyl, (C<sub>1</sub>-C<sub>6</sub>)alkylcarbonyl, phenacyl or  
 13 substituted phenacyl group; or, when n = 0, R<sup>1</sup>  
 14 represents SR<sup>X</sup>, wherein R<sup>X</sup> represents a group:

15

16

17

18

19

20

21

22 R<sup>2</sup> represents a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
 23 alk enyl, phenyl (C<sub>1</sub>-C<sub>6</sub>) alkyl, cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl or cycloalkenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl  
 24 group;

25

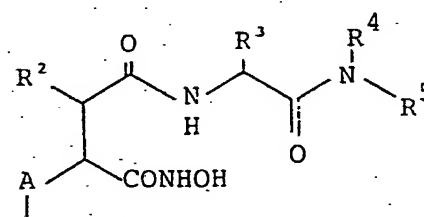
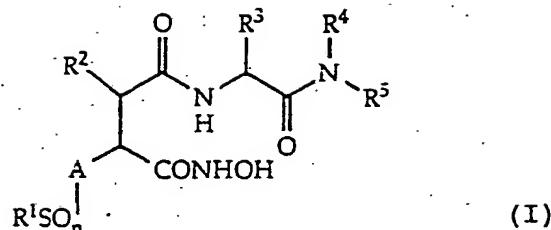
26 R<sup>3</sup> represents an amino acid side chain or a C<sub>1</sub>-C<sub>6</sub>  
 27 alkyl, benzyl, (C<sub>1</sub>-C<sub>6</sub> alkoxy)benzyl, benzyloxy(C<sub>1</sub>-C<sub>6</sub> alkyl) or benzyloxybenzyl group;

28

31 R<sup>4</sup> represents a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl group;

32

33 R<sup>5</sup> represents a hydrogen atom or a methyl group;



1 n is an integer having the value 0, 1 or 2; and

2  
3 A represents a C<sub>1</sub>-C<sub>6</sub> hydrocarbon chain, optionally  
4 substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl  
5 or substituted phenyl groups;

6  
7 or a salt thereof.

8  
9 Hereafter in this specification, the term "compound"  
10 includes "salt" unless the context requires otherwise.

11  
12 As used herein the term "C<sub>1</sub>-C<sub>6</sub> alkyl" refers to a  
13 straight or branched chain alkyl moiety having from  
14 one to six carbon atoms, including for example,  
15 methyl, ethyl, propyl, isopropyl, butyl, t-butyl,  
16 pentyl and hexyl, and cognate terms. (such as "C<sup>1</sup>-C<sup>6</sup>  
17 alkoxy") are to be construed accordingly.

18  
19 The term "C<sub>1</sub>-C<sub>6</sub> alkenyl" refers to a straight or  
20 branched chain alkyl moiety having one to six carbons  
21 and having in addition one double bond, of either E or  
22 Z stereochemistry where applicable. This term would  
23 include, for example, an alpha, beta-unsaturated  
24 methylene group, vinyl, 1-propenyl, 1- and 2-butenyl  
25 and 2-methyl-2-propenyl.

26  
27 The term "cycloalkyl" refers to a saturated  
28 alicyclic moiety having from 3 to 8 carbon atoms  
29 and includes for example, cyclopropyl, cyclobutyl,  
30 cyclopentyl and cyclohexyl.

31

32

33

1    The term "cycloalkenyl" refers to an unsaturated  
2    alicycle having from 3 to 8 carbon atoms and includes  
3    cyclopropenyl, cyclobutenyl and cyclopentenyl,  
4    cyclohexenyl.

5

6    The term "substituted", as applied to a phenyl or other  
7    aromatic ring, means substituted with up to four  
8    substituents each of which independently may be C<sub>1</sub>-C<sub>6</sub>  
9    alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, hydroxy, thiol, C<sub>1</sub>-C<sub>6</sub> alkylthiol,  
10   amino, halo (including fluoro, chloro, bromo and iodo),  
11   trifluoromethyl or nitro.

12

13   The term "amino acid side chain" means a characteristic  
14   side chain attached to the -CH(NH<sub>2</sub>)(COOH) moiety in the  
15   following R or S amino acids: glycine, alanine, valine,  
16   leucine, isoleucine, phenylalanine, tyrosine,  
17   tryptophan, serine, threonine, cysteine, methionine,  
18   asparagine, glutamine, lysine, histidine, arginine,  
19   glutamic acid and aspartic acid.

20

21   The term "hydrocarbon chain" includes alkylene,  
22   alkenylene and alkynylene chains of from 1 to 6 carbon  
23   atoms. Preferably the carbon atom of the hydrocarbon  
24   chain nearest to the hydroxamic acid group is a  
25   methylene carbon atom.

26

27   There are several chiral centres in the compounds  
28   according to the invention because of the presence of  
29   asymmetric carbon atoms. The presence of several  
30   asymmetric carbon atoms gives rise to a number of  
31   diastereomers with the appropriate R or S  
32   stereochemistry at each chiral centre. General formula  
33   I and, where appropriate, all other formulae in this

1 specification are to be understood to include all such  
2 stereoisomers and mixtures (for example racemic  
3 mixtures) thereof. Compounds in which the chiral centre  
4 adjacent the substituent R<sup>3</sup> has S stereochemistry  
5 and/or the chiral centre adjacent the substituent R<sup>2</sup>  
6 has R stereochemistry are preferred.

7  
8 Further or other preferred compounds include those in  
9 which, independently or in any combination:

10  
11 R<sup>1</sup> represents a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl,  
12 phenyl, thiophenyl, benzyl, acetyl or benzoyl  
13 group;

14  
15 R<sup>2</sup> represents a C<sub>3</sub>-C<sub>6</sub> alkyl (for example isobutyl)  
16 group;

17  
18 R<sup>3</sup> represents a benzyl or 4-(C<sub>1</sub>-C<sub>6</sub>)alkoxyphenylmethyl  
19 or benzyloxybenzyl group;

20  
21 R<sup>4</sup> represents a C<sub>1</sub>-C<sub>4</sub> alkyl (for example methyl)  
22 group; and

23  
24 R<sup>5</sup> represents a hydrogen atom.

25  
26 Particularly preferred compounds include:

27  
28 1. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthio-  
29 methyl)-succinyl]-L-phenylalanine-N-methylamide,

30  
31 2. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenyl-  
32 thio-methyl)succinyl]-L-phenylalanine-  
33 N-methylamide,

- 1     3. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzylthio-  
2       methyl) succinyl]-L-phenylalanine-N-methylamide,
- 3
- 4     4. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(acetylthio-  
5       methyl) succinyl]-L-phenylalanine-N-methylamide and
- 6
- 7     5. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiomethyl)  
8       succinyl]-L-phenylalanine-N-methylamide
- 9
- 10    6. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzoylthio-  
11      methyl) succinyl]-L-phenylalanine-N-methylamide
- 12
- 13    7. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(pivaloyl-  
14      thiomethyl) succinyl]-L-phenylalanine-N-methyl-  
15      amide
- 16
- 17    8. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenyl-  
18      thiomethyl) succinyl]-L-phenylalanine-N-methyl-  
19      amide sodium salt
- 20
- 21    9. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxy-  
22      phenyl-thiomethyl) succinyl]-L-phenylalanine-N-  
23      methylamide
- 24
- 25    10. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxy-  
26      phenylthiomethyl) succinyl]-L-phenylalanine-N-  
27      methylamide
- 28
- 29    11. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thio-  
30      phenethiomethyl) succinyl]-L-phenylalanine-N-  
31      methylamide sodium salt
- 32
- 33

1       12. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxy-  
2           phenylthiomethyl)succinyl]-L-phenylalanine-N-  
3           methylamide sodium salt  
4  
5       13. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-tert-  
6           butylphenylthiomethyl)succinyl]-L-phenylalanine-  
7           N-methylamide  
8  
9       14. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2,4-di-  
10           methylphenylthiomethyl)succinyl]-L-phenyl-  
11           alanine-N-methylamide  
12  
13      15. bis-S,S'-{[4-(N-Hydroxyamino)-2R-isobutyl-  
14           3S-(thiomethyl)succinyl]-L-phenylalanine-N-methyl-  
15           amide} disulphide  
16  
17      16. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-bromo-  
18           phenylthio-methyl)succinyl]-L-phenylalanine-N-  
19           methylamide  
20  
21      17. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-chloro-  
22           phenylthiomethyl)succinyl]-L-phenylalanine-N-  
23           methylamide  
24  
25      18. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-methyl-  
26           phenylthiomethyl)succinyl]-L-phenylalanine-N-  
27           methylamide  
28  
29      19. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-  
30           aminophenylthiomethyl)succinyl]-L-phenylalanine-  
31           N-methylamide  
32  
33

- 1    20. [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenyl-  
2       sulphinylmethylsuccinyl]-L-phenylalanine-N-methyl-  
3       amide  
4
- 5    21. [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenyl-  
6       sulphonylmethylsuccinyl]-L-phenylalanine-N-methyl-  
7       amide  
8
- 9    22. [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenyl-  
10      sulphinylmethylsuccinyl]-L-phenylalanine-N-  
11      methylamide  
12
- 13   23. [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenyl-  
14      sulphonylmethylsuccinyl]-L-phenylalanine-N-  
15      methylamide  
16
- 17   24. [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenyl-  
18      sulphonylmethylsuccinyl]-L-phenylalanine-N-  
19      methylamide sodium salt  
20
- 21   25. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutyl-  
22       oxycarbonylamino)phenyl)thiomethylsuccinyl]-L-  
23       phenylalanine-N-methylamide  
24
- 25   26. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl-N-  
26       (tert-butoxycarbonyl)-glycylamino)phenyl)thio-  
27       methylsuccinyl]-L-phenylalanine-N-methylamide  
28
- 29       and, where appropriate, their salts. Compounds 2 and 5  
30       are especially preferred and compound 2 is the most  
31       preferred, because of its good collagenase-inhibiting  
32       and protoglycanase-inhibiting activities.  
33

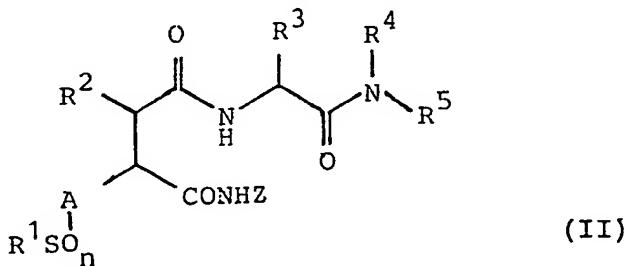
1 Compounds of general formula I may be prepared by any  
 2 suitable method known in the art and/or by the  
 3 following process, which itself forms part of the  
 4 invention.

5

6 According to a second aspect of the invention, there is  
 7 provided a process for preparing a compound of general  
 8 formula I as defined above, the process comprising:

9

10 (a) deprotecting a compound of general formula II



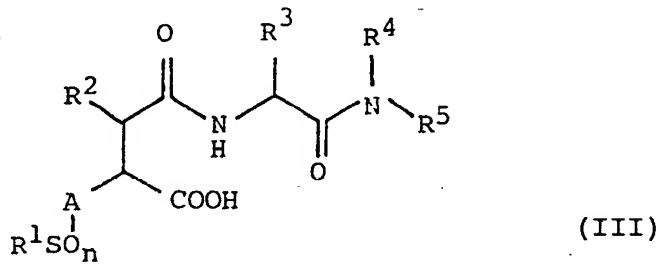
18 wherein:

19

20 R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, A and n are as defined in  
 21 general formula I and Z represents a protective  
 22 group such as a benzyl group; or

23

24 (b) reacting a compound of general formula III



32 wherein:

33

1        R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, A and n are as defined in  
2        general formula I,

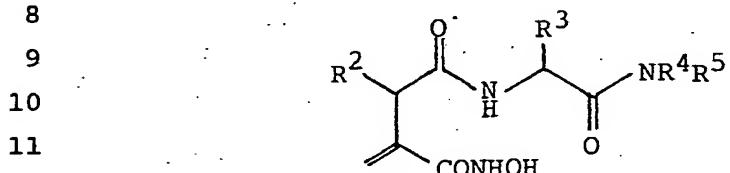
3

4        with hydroxylamine or a salt thereof; or

5

6        (c) reacting a compound of general formula VIA

7



13

14        wherein

15

16        R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined in general  
17        formula I,

18

19        either with a thiol of the general formula R<sup>1</sup>S, wherein  
20        R<sup>1</sup> is as defined in general formula I to give a  
21        compound of general formula I in which A represents a  
22        methylene group and n is 0,

23

24        or with a cuprate of the general formula (R<sup>1</sup>S-A<sup>1</sup>)<sub>2</sub>CuLi,  
25        wherein R<sup>1</sup> is as defined in general formula I and A<sup>1</sup> is  
26        such that -A<sup>1</sup>-CH<sub>2</sub>- is identical to -A-, as defined in  
27        general formula I.

28

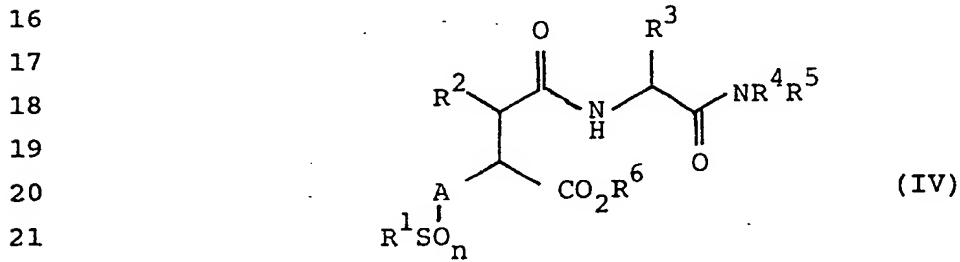
29        (d) optionally after step (a), step (b) or step (c)  
30        converting a compound of general formula I into another  
31        compound of general formula I.

32

33

1 Compounds of general formula I which are sulphoxides or  
 2 sulphones can be derived from thiol compounds of  
 3 general formula I by oxidation. Alternatively, thiols  
 4 of general formula II or III may be oxidised.  
 5 Compounds of general formula I which are disulphides  
 6 (ie compounds wherein R<sup>1</sup> represents SR<sup>X</sup>) may be derived  
 7 from thiol esters of general formula I by milk  
 8 oxidation, for example in air.

9 .  
 10 A compound of general formula II may be prepared from a  
 11 compound of general formula III by reaction with an  
 12 O-protected (such as benzyl) hydroxylamine. A compound  
 13 of general formula III may be prepared by  
 14 desterification (such as hydrolysis) of an ester of the  
 15 general formula IV



22 wherein:

23 .  
 24 R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, A and n are as defined in  
 25 general formula I and R<sup>6</sup> represents C<sub>1</sub>-C<sub>6</sub> alkyl,  
 26 phenyl C<sub>1</sub>-C<sub>6</sub> alkyl or substituted phenyl C<sub>1</sub>-C<sub>6</sub>  
 27 alkyl.

28 .  
 29 A compound of general formula IV can be prepared from  
 30 an ester of general formula V or an acid of general  
 31 formula VI

32 .

33 .

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9 wherein:

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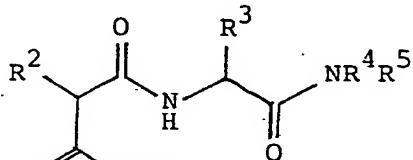
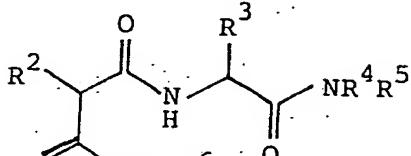
29

30

31

32

33



$R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined in general formula I and  $R^6$  represents  $C_1-C_6$  alkyl, phenyl  $C_1-C_6$  alkyl or substituted phenyl  $C_1-C_6$  alkyl

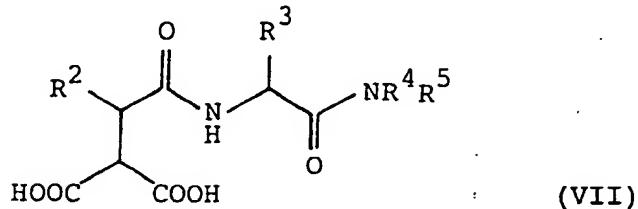
by reaction with a thiol  $R^1SH$ , wherein  $R^1$  is as defined in general formula I, to give compounds wherein A represents a methylene group,

or by reaction with a cuprate of the general formula  $(R^1S-A^1)_2CuLi$ , wherein  $R^1$  is as defined in general formula I and  $A^1$  is such that  $-A^1-CH_2-$  is identical to  $-A-$ , as defined in general formula I.

Esters of general formula V can be prepared by esterifying acids of general formula VI with an appropriate alcohol  $R^6OH$  or other esterifying agent.

Compounds of general formula VIA can be prepared by reacting compounds of general formula VI with hydroxylamine or a salt thereof.

1 An acid of general formula VI can be prepared by  
 2 reacting a malonic acid derivative of general formula  
 3 VII

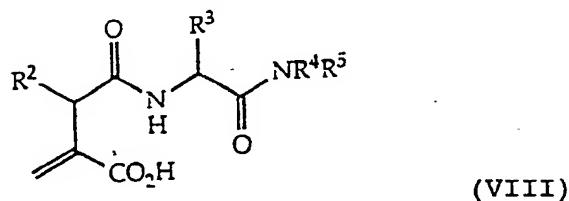


wherein:

$R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined in general formula I

with formaldehyde in the presence of pyridine.

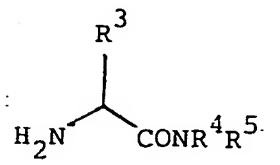
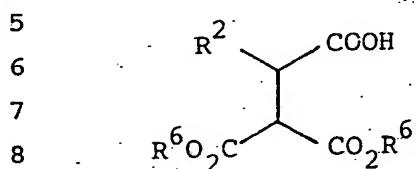
An acid of general formula VII can in turn be prepared by desterifying (for example hydrolysing) a compound of general formula VIII



wherein:

$R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined in general formula I and  $R^6$  represents  $C_1-C_6$  alkyl, phenyl  $C_1-C_6$  alkyl or substituted phenyl  $C_1-C_6$  alkyl.

1 A compound of general formula VIII can be prepared by  
2 reacting a compound of general formula IX with a  
3 compound of general formula X

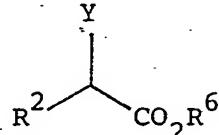


10  
11 wherein:

13         $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined in general  
14        formula I and  $R^6$  represents  $C_1-C_6$  alkyl, phenyl  
15         $C_1-C_6$  alkyl or substituted phenyl  $C_1-C_6$  alkyl.

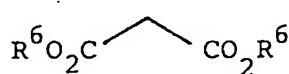
17 The starting materials and other reagents are either  
18 available commercially or can be synthesised by simple  
19 chemical procedures.

21 For example, a substituted acid of general formula IX  
22 may be prepared by reacting an ester of the general  
23 formula XI . . .



(xi)

wherein Y represents halo and R<sup>5</sup> is as defined above  
and R<sup>2</sup> and R<sup>6</sup> as defined above, with a malonate  
derivative of the general formula XII



1 wherein R<sup>6</sup> is as defined above with the proviso that  
2 when R<sup>6</sup> is aromatic in general formula XI it is  
3 aliphatic in general formula XII or vice versa, and  
4 selectively de-esterifying.

5  
6 Compounds of general formula XI can simply be derived  
7 from amino acids, which can be obtained in  
8 enantiomerically pure form, enabling a choice of  
9 optically active compounds of general formula I to be  
10 prepared.

11  
12 Compounds of general formulae II and III are valuable  
13 intermediates in the preparation of compounds of  
14 general formula I. According to a third aspect of the  
15 invention, there is therefore provided a compound of  
16 general formula II. According to a fourth aspect of the  
17 invention, there is provided a compound of general  
18 formula III.

19  
20 As mentioned above, compounds of general formula I are  
21 useful in human or veterinary medicine as they are  
22 active inhibitors, of metalloproteases involved in  
23 tissue degradation.

24  
25 According to a fifth aspect of the invention, there is  
26 provided a compound of general formula I for use in  
27 human or veterinary medicine, particularly in the  
28 management (by which is meant treatment or prophylaxis)  
29 of disease involving tissue degradation, in particular  
30 rheumatoid arthritis, and/or in the promotion of wound  
31 healing.

32  
33

1 According to a sixth aspect of the invention, there is  
2 provided the use of a compound of general formula I in  
3 the preparation of an agent for the management of  
4 disease involving tissue degradation, particularly  
5 rheumatoid arthritis, and/or in the promotion of wound  
6 healing. Compounds of general formula I can therefore  
7 be used in a method of treating disease involving  
8 tissue degradation, particularly rheumatoid arthritis,  
9 and/or in a method of promoting wound healing, the  
10 method in either case comprising administering to a  
11 human or animal patient an effective amount of a  
12 compound of general formula I.

13

14 The potency of compounds of general formula I to act  
15 as inhibitors of collagenase (a metalloprotease  
16 involved in tissue degradation) was determined by the  
17 procedure of Cawston and Barrett, (Anal. Biochem., 99,  
18 340-345, 1979) and their potency to act as inhibitors  
19 of stromelysin was determined using the procedure of  
20 Cawston et al (Biochem. J., 195, 159-165 1981), both of  
21 which techniques are to be described more fully in the  
22 examples and are incorporated by reference herein so  
23 far as the law allows.

24

25 According to a seventh aspect of the invention, there  
26 is provided a pharmaceutical or veterinary formulation  
27 comprising a compound of general formula I and a  
28 pharmaceutically and/or veterinarily acceptable  
29 carrier. One or more compounds of general formula I may  
30 be present in association with one or more non-toxic  
31 pharmaceutically and/or veterinarily acceptable  
32 carriers and/or diluents and/or adjuvants and if  
33 desired other active ingredients.

1 According to an eighth aspect of the invention, there  
2 is provided a process for the preparation of a  
3 pharmaceutical or veterinary formulation in accordance  
4 with the seventh aspect, the process comprising  
5 admixing a compound of general formula I and a  
6 pharmaceutically and/or veterinarily acceptable  
7 carrier.

8

9 Compounds of general formula I may be formulated for  
10 administration by any route and would depend on the  
11 disease being treated. The compositions may be in  
12 the form of tablets, capsules, powders, granules,  
13 lozenges, liquid or gel preparations, such as oral,  
14 topical, or sterile parental solutions or  
15 suspensions.

16

17 Tablets and capsules for oral administration may be in  
18 unit dose presentation form, and may contain  
19 conventional excipients such as binding agents, for  
20 example syrup, acacia, gelatin, sorbitol, tragacanth,  
21 or polyvinyl-pyrollidone; fillers for example lactose,  
22 sugar, maize-starch, calcium phosphate, sorbitol or  
23 glycine; tabletting lubricant, for example magnesium  
24 sterate, talc, polyethylene glycol or  
25 silica; disintegrants, for example potato starch, or  
26 acceptable wetting agents such as sodium lauryl  
27 sulphate. The tablets may be coated according to  
28 methods well known in normal pharmaceutical practice.  
29 Oral liquid preparations may be in the form of, for  
30 example, aqueous or oily suspensions, solutions,  
31 emulsions, syrups or elixirs, or may be presented as a  
32 dry product for reconstitution with water or other  
33 suitable vehicle before use. Such liquid

1 preparations may contain conventional additives such  
2 as suspending agents, for example sorbitol, syrup,  
3 methyl cellulose, glucose syrup, gelatin,  
4 hydrogenated edible fats; emulsifying agents, for  
5 example lecithin, sorbitan monooleate, or acacia;  
6 non-aqueous vehicles (which may include edible  
7 oils), for example almond oil, fractionated coconut  
8 oil, oily esters such as glycerine, propylene glycol,  
9 or ethyl alcohol; preservatives, for example methyl or  
10 propyl p-hydroxybenzoate or sorbic acid, and if  
11 desired conventional flavouring or colouring agents.

12  
13 The dosage unit involved in oral administration may  
14 contain from about 1 to 250 mg, preferably from about  
15 25 to 250 mg of a compound of general formula I. A  
16 suitable daily dose for a mammal may vary widely  
17 depending on the condition of the patient. However,  
18 a dose of a compound of general formula I of about 0.1  
19 to 300mg/kg body weight, particularly from about 1 to  
20 100 mg/kg body weight may be appropriate.

21  
22 For topical application to the skin the drug may be  
23 made up into a cream, lotion or ointment. Cream or  
24 ointment formulations that may be used for the drug  
25 are conventional fomulations well known in the art,  
26 for example, as described in standard text books of  
27 pharmaceutics such as the British Pharmacopoeia.

28  
29 For topical applications to the eye, the drug may be  
30 made up into a solution or suspension in a suitable  
31 sterile aqueous or non-aqueous vehicle. Additives,  
32 for instance buffers such as sodium metabisulphite or  
33 disodium edeate; preservatives including bactericidal

1 and fungicidal agents, such as phenyl mercuric  
2 acetate or nitrate, benzalkonium chloride or  
3 chlorhexidine, and thickening agents such as  
4 hypromellose may also be included.

5  
6 The dosage employed for the topical administration  
7 will, of course, depend on the size of the area being  
8 treated. For the eyes each dose will be typically in  
9 the range from 10 to 100 mg of the compound of general  
10 formula I.

11  
12 The active ingredient may also be administered  
13 parenterally in a sterile medium. The drug  
14 depending on the vehicle and concentration used, can  
15 either be suspended or dissolved in the vehicle.  
16 Advantageously, adjuvants such as a local anesthetic,  
17 preservative and buffering agents can be dissolved in  
18 the vehicle.

19  
20 For use in the treatment of rheumatoid arthritis the  
21 compounds of this invention can be administered by  
22 the oral route or by injection intra-articularly into  
23 the affected joint. The daily dosage for a 70 kg  
24 mammal will be in the range of 10 mgs to 1 gram of a  
25 compound of general formula I.

26  
27 The following examples illustrate the invention, but  
28 are not intended to limit the scope in any way. The  
29 following abbreviations have been used in the  
30 Examples:-

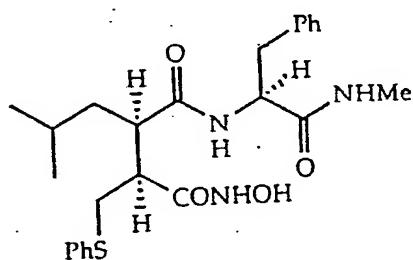
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|    |       |                                               |
|----|-------|-----------------------------------------------|
| 1  | DCC   | - Dicyclohexylcarbodiimide                    |
| 2  | DCM   | - Dichloromethane                             |
| 3  | DCU   | - Dicyclohexylurea                            |
| 4  | DIPE  | - Diisopropyl ether                           |
| 5  | DMF   | - N,N-dimethylformamide                       |
| 6  | HOBT  | - Hydroxybenztriazole                         |
| 7  | NMM   | - N-Methylmorpholine                          |
| 8  | TFA   | - Trifluoroacetic acid                        |
| 9  | THF   | - Tetrahydrofuran                             |
| 10 | WSCDI | - N-(Dimethylaminoethyl)-N'-ethylcarbodiimide |

12 Examples 1

13

14 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)-  
15 succinyl]-L-phenylalanine-N-methylamide



23 a) 2R-Bromo-5-methylpentanoic acid.

24

25 D-Leucine (100g, 0.76 mol) and potassium bromide  
 26 (317.5g, 2.67 mol) were dissolved in aqueous acid  
 27 (150ml concentrated sulphuric acid in 500ml of water).  
 28 The solution was cooled to -2° and sodium nitrite  
 29 (69.6g, 0.95 mol in water) was added over 1h taking  
 30 care to maintain the temperature between -1 and -2°.  
 31 After addition was complete the mixture was kept at 0°  
 32 for a further hour, then DCM was added and the mixture  
 33 stirred for a few minutes. The layers were separated

1 and the aqueous phase was washed with further portions  
2 of DCM (5 x 250ml). The combined organic layers  
3 were dried over magnesium sulphate then the solvent  
4 removed to give the acid as a pale yellow oil (123.1g,  
5 0.63 mol, 83%)

6

7  $[\alpha]_D = +38.0^\circ$  (c = 2, methanol)

8

9  $\delta_H$  (250 MHz,  $CDCl_3$ ) 4.29 (1H, t, J = 6.5Hz,  
10  $BrCHCO_2H$ ), 1.91 (2H, t, J = 7Hz,  $CHCH_2CH$ ), 1.83 (1H, m,  
11  $Me_2CH$ ), and 0.94 (6H, 2xd, J = 7Hz,  $(CH_3)_2CH$ )

12

13 b) tert-Butyl 2R-Bromo-5-methylpentanoate.

14

15 2R-Bromo-5-methylpentanoic acid (123g, 0.63 mol)  
16 was dissolved in DCM (400ml) and the solution cooled  
17 to  $-40^\circ$  while isobutene was condensed in to roughly  
18 double the volume. Maintaining the temperature at  
19  $-40^\circ$  concentrated sulphuric acid (4ml) was added  
20 dropwise. When the addition was complete the  
21 reaction was allowed to warm to room temperature  
22 overnight. The resultant solution was concentrated  
23 to half the volume by removing the solvent at reduced  
24 pressure, then the DCM was washed twice with an equal  
25 volume of 10% sodium bicarbonate solution. The organic  
26 layer was dried over magnesium sulphate and the  
27 solvent removed under reduced pressure to leave the  
28 title compound as a yellow oil (148.0g, 0.59 mol, 94%).

29

30  $[\alpha]_D = +23.0^\circ$  (c = 2, methanol)

31

32

33

1   delta<sub>H</sub> (250 MHz, CDCl<sub>3</sub>) 4.18 (1H, t, J= 6.5Hz,  
2   BrCHCO<sub>2</sub>H), 1.89 (2H, m, CHCH<sub>2</sub>CH), 1.78 (1H, m, Me<sub>2</sub>CH),  
3   1.49 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C) and 0.94 (6H, 2xd, J= 7Hz,  
4   (CH<sub>3</sub>)<sub>2</sub>CH)

5

6   delta<sub>C</sub> (63.9 MHz, CDCl<sub>3</sub>) 167.0, 82.0, 46.3, 43.4,  
7   27.6, 26.3, 22.2, and 21.6.

8

9   c) Benzyl (2-benzloxycarbonyl-3R-(tert-butoxycarbonyl)-  
10   5-methylhexanoate.

11

12   Dibenzyl malonate (124.5g, 0.44 mol) was taken up in  
13   dry DMF and potassium tert-butoxide (49.2g, 0.44  
14   mol) was added portionwise with stirring and cooling.  
15   When a homogeneous solution had formed it was cooled to  
16   0° then tert-butyl-2R-bromo-5-methylpentanoate  
17   (110.0g, 0.44 mol) in DMF (200 ml) was added dropwise  
18   over 1h. When addition was complete the reaction was  
19   transferred to a cold room at <5° and left for 4 days.  
20   The reaction mixture was partitioned between ethyl  
21   acetate and saturated ammonium chloride then the  
22   aqueous layer extracted with further ethyl acetate  
23   (4x500ml), drying and solvent removal left an oil  
24   (228g) heavily contaminated with DMF. This oil was  
25   taken into ether (1 litre) and washed with brine  
26   (2x1l) then the organic layer dried (magnesium  
27   sulphate), solvent removed under reduced pressure to  
28   leave the desired material (179g) contaminated with a  
29   small amount of dibenzyl malonate.

30

31   [alpha]<sub>D</sub> = +22.5° (c = 2, methanol)

32

33

1   delta<sub>H</sub> (250 MHz, CDCl<sub>3</sub>) 7.40 - 7.25 (10H, m, Aromatic  
2   H), 5.14 (4H, 2xABq, CH<sub>2</sub>Ph), 3.77 (1H, d, J= 10Hz,  
3   BnO<sub>2</sub>CCHCO<sub>2</sub>Bn), 3.09 (1H, dt, J= 10,6Hz,  
4   CH<sub>2</sub>CHCO<sub>2</sub>tBu), 1.50 (3H, m, CH<sub>2</sub> + CHMe<sub>2</sub>) 1.41 (9H, s,  
5   C(CH<sub>3</sub>)<sub>3</sub>) and 0.88 (6H, 2xd, J= 7Hz).

6

7   d) [4-Benzylxyloxy-3-benzylloxycarbonyl-2R-isobutyl-  
8   succinyl]-L-phenylalanine-N-methylamide

9

10   Benzyl(2-benzylloxycarbonyl-5-methyl-3R-tert-butoxycarb-  
11   onyl)-hexanoate (281.4g, 0.56 mol) was taken up in 5%  
12   water in TFA (410 ml) and allowed to stand at 5°  
13   overnight. After this time the TFA was evaporated  
14   under reduced pressure then the residue partitioned  
15   between DCM (1l) and brine (200ml). Solvent removal  
16   left an oil which crystallised on standing (230g).

17

18   The crude acid from this reaction was dissolved in DMF  
19   (1l), then HOBT (95.3g, 0.64 mol), NMM (64g, 0.64 mol)  
20   and phenylalanine-N-methylamide (113.0g, 0.64 mol) were  
21   added at room temperature. The mixture was cooled  
22   to 0° before dropwise addition of DCC (131.0g, 0.64  
23   mol) in THF (1l). This solution was stirred to room  
24   temperature over the weekend. The precipitated DCU was  
25   removed by filtration then the solvents were removed  
26   from the filtrate under reduced pressure to leave an  
27   oil. This oily residue was dissolved in ethyl acetate  
28   then washed with 10% citric acid, 10% sodium  
29   bicarbonate and saturated brine. The organic layer was  
30   dried (magnesium sulphate), filtered then the solvent  
31   removed under reduced pressure to give the title  
32   compound as an oil (400g). This material was columned  
33   on silica using gradient elution (0 - 50% ethyl

1 acetate in hexane) to remove impurities and separate  
2 a small amount of the minor diastereoisomer. The  
3 material from the column (195g) was recrystallised  
4 from DIPE to give the title compound as a white  
5 crystalline solid (140.2g, 0.25 mol, 47%)

6

7 m.p. 98 -99°

8 Analysis calculated for C<sub>33</sub>H<sub>38</sub>N<sub>2</sub>O<sub>6</sub>

9 Requires C 70.95 H 6.86 N 5.01

10 Found C 70.56 H 6.89 N 5.06

11

12 delta<sub>H</sub> (250MHz, CDCl<sub>3</sub>) 7.42 - 7.13 (15H, m, Aromatic  
13 H), 6.58 (1H, d, J=7.7Hz, CONH), 5.75 (1H, m,  
14 CONHMe), 5.20 - 5.05 (4H, m, OCH<sub>2</sub>Ph), 4.50 (1H, dt, J=  
15 6.9, 7.7Hz, CHCH<sub>2</sub>Ph), 3.79 (1H, d, J= 9.1Hz,  
16 CH(CO<sub>2</sub>Bn)), 3.15 - 2.91 (2H, m, CH<sub>2</sub>Ph), 2.65 (3H, d, J=  
17 4.8Hz, CONHCH<sub>3</sub>), 1.52 (1H, m, CHCH<sub>2</sub>CH), 1.32 (1H, m,  
18 CH(CH<sub>3</sub>)), 1.05 (1H, m, CHCH<sub>2</sub>CH), and 0.74 (6H, 2xd, J=  
19 6.5Hz, CH(CH<sub>3</sub>)<sub>2</sub>)

20

21 e) [4-Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-phenyl-  
22 alanine-N-methylamide.

23

24 [4-Benzylxy-3-benzylxycarbonyl-2R-isobutylsuccinyl]-  
25 L-phenylalanine-N-methylamide (29.6g, 53mmol) was taken  
26 up in ethanol, ammonium formate (16.7g, 265mmol) added  
27 followed by 10% palladium on charcoal (6g) as a  
28 slurry in isopropyl alcohol. After 30 minutes at room  
29 temperature the catalyst was removed by filtration,  
30 then washed with ethanol to give a solution of the  
31 crude diacid. To this was added piperidine (5.0g) and  
32 the mixture stirred at room temperature for 15 minutes  
33 before addition of aqueous formaldehyde (40%

1 solution, 25ml). After 18 hours at room temperature  
2 the mixture was refluxed for 1 h. Solvents were  
3 removed under reduced pressure and the residue  
4 partitioned between ethyl acetate and citric acid.  
5 The acid layer was extracted with further portions of  
6 ethyl acetate (2x250ml), the combined organic layers  
7 were extracted with potassium carbonate (3x200ml).  
8 These base extracts were acidified to pH 4 and  
9 re-extracted with DCM then the organic layer dried  
10 over magnesium sulphate. Solvent removal  
11 under reduced pressure gave the desired product as a  
12 white solid (9.35g, 27.0mmol, 51%).

13

14 m.p. 149-151°C

15

16  $\delta_H$  (250MHz,  $CDCl_3$ ) 8.37 (2H, d,  $J = 9.0\text{Hz}$ , CONH),  
17 7.39 (1H, m, CONHMe), 7.27 - 7.06 (5H, m, Aromatic  
18 H), 6.40 (1H, s,  $CH_2CHCO_2H$ ), 5.78 (1H, s,  $CH_2CHCO_2H$ ),  
19 4.93 (1H, q,  $J = 7\text{Hz}$ ,  $CHCH_2Ph$ ), 3.92 (1H, m,  $CH_2CHCONH$ ),  
20 2.95 (2H, m,  $CH_2Ph$ ), 2.71 (3H, d,  $J = 4.1\text{Hz}$ , NHCH<sub>3</sub>),  
21 1.68 (1H, m), 1.45 (2H, m), and 0.86 (6H, 2xd,  $J =$   
22 5.8Hz,  $CH(CH_3)_2$ ).

23

24  $\delta_C$  (63.9Hz,  $CDCl_3$ ) 173.3, 172.8, 169.6, 139.1,  
25 136.3, 129.2, 128.3, 127.0, 126.6, 54.4, 43.5, 41.4,  
26 39.1, 26.2, 25.7, 22.5 and 22.4

27

28 f) [4-Hydroxy-2R-isobutyl-3S-(phenylthiomethyl)-  
29 succinyl]-L-phenylalanine-N-methylamide

30

31 [4-Hydroxy-2R-isobuty-3-ethenylsuccinyl]-L-phenyl-  
32 alanine-N-methylamide (15.0g, 44mmol) was dissolved in  
33 thiophenol

1 (150ml) and the mixture stirred in the dark under  
2 nitrogen at 60° for 2 days. Ether was added to the  
3 cooled reaction mixture and the precipitated product  
4 collected by filtration. The solid was washed with  
5 large volumes of ether and dried under vacuum to give  
6 the title compound (13.1g, 28.7mmol, 65%).

7

8 m.p. 199-201°C

9 Analysis calculated for C<sub>25</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>S  
10 Requires C 65.76 H 7.06 N 6.14 S 7.02  
11 Found C 65.69 H 7.06 N 6.07 S 7.05

12

13 delta<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO) 8.40 (1H, d, J= 9Hz, CONH),  
14 7.82 (1H, m, CONHMe), 7.35 - 7.10 (7H, m, Aromatic  
15 H), 7.04 (3H, m, Aromatic H), 4.62 (1H, m, CHCH<sub>2</sub>Ph),  
16 2.94 (1H, dd, J= 14,5Hz, CHCH<sub>2</sub>Ph), 2.89 (1H, dd, J=  
17 14,9Hz, CHCH<sub>2</sub>Ph), 2.62 (3H, d, J= 4.5Hz, CONHCH<sub>3</sub>), 2.41  
18 (3H, m, 2xCH + CH<sub>2</sub>SPh), 2.23 (1H, d, J= 12Hz, CH<sub>2</sub>SPh),  
19 1.43 (1H, m, CHCH<sub>2</sub>CH), 1.30 (1H, bm, CH(CH<sub>3</sub>)<sub>2</sub>), 0.90  
20 (1H, m, CHCH<sub>2</sub>CH) and 0.78 (6H, 2xd, J= 6.5Hz, CH(CH<sub>3</sub>)<sub>2</sub>).  
21

22 g) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthio-  
23 methyl) succinyl]-L-phenylalanine-N-methylamide

24

25 [4-Hydroxy-2R-isobutyl-3S-(phenylthiomethyl)succinyl]-  
26 L-phenylalanine-N-methylamide (16.8g, 37 mmol) and  
27 HOBT (6.6g, 44 mmol) were dissolved in DCM / DMF  
28 (4:1) and the mixture cooled to 0° before adding WSCDI  
29 (8.5g, 44 mmol) and NMM (4.5g, 44 mmol). The mixture  
30 was stirred at 0° for 1h to ensure complete formation  
31 of the activated ester. Hydroxylamine hydrochloride  
32 (3.8g, 55 mmol) and NMM (5.6g, 55 mmol) were dissolved  
33 in DMF then this mixture added dropwise to the cooled

1 solution of the activated ester. After 1h the reaction  
2 was poured into ether / water (1:1) whereupon the  
3 desired product precipitated as white crystals. These  
4 were collected by filtration, further washed with ether  
5 and water then dried under vacuum at 50°. This  
6 material was recrystallised from methanol / water (1:1)  
7 to remove a trace of the minor diastereomer (9.03g,  
8 19.2 mmol, 52%).

9

10 m.p. 227-229°C

11

12  $[\alpha]_D = -88^\circ$  (c = 10 , methanol)

13

14  $\delta_H$  (250MHz, D<sub>6</sub>-DMSO) 8.84 (1H, d, J= 1.5Hz, NHOH),  
15 8.35 (1H, d, J= 8.7Hz, CONH), 7.87 (1H, m, CONHMe),  
16 7.29 - 6.92 (11H, m, Aromatic H + NHOH), 4.60 (1H, m,  
17 CHCH<sub>2</sub>Ph), 2.94 (1H, dd, J= 13.5,4.3, CHCH<sub>2</sub>Ph), 2.77  
18 (1H, dd, J= 13.5,10, CHCH<sub>2</sub>Ph), 2.60 (3H, d, J= 4.6Hz),  
19 2.53 (1H, m), 2.41 (1H, m), 2.20 (1H, dd, J= 13.4,2.2Hz,  
20 CH<sub>2</sub>SPh), 2.09 (1H, dd, J=13.4,2.4Hz,  
21 CH<sub>2</sub>SPh), 1.38 (2H, m, CHMe<sub>2</sub> + CHCH<sub>2</sub>CH), 0.88 (1H,  
22 m, CHCH<sub>2</sub>CH), 0.82 (3H, d, J= 6.4Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and 0.74  
23 (3H, d, J+ 6.4Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

24

25  $\delta_C$  (63.9MHz, D<sub>6</sub>-DMSO) 172.9, 171.6, 166.3, 138.1,  
26 136.7, 129.1, 128.9, 128.0, 127.3, 126.4, 125.2, 54.2,  
27 46.4, 46.0, 37.7, 32.4, 25.6, 25.2, 24.2, and 21.7.

28

29

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31

32

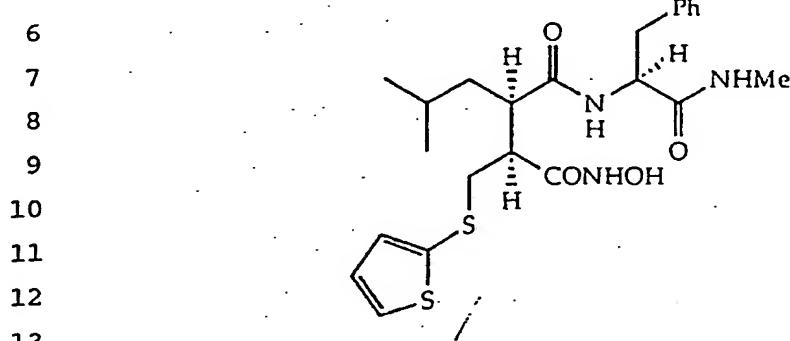
33

1    Example 2

2

3    [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiometh-  
4    yl) succinyl]-L-phenylalanine-N-methylamide

5



11

12

13

14    a) [4-N-Hydroxy-2R-isobutyl-3S-(thiophenylthiomethyl)  
15    succinyl]-L-phenylalanine-N-methylamide

16

17    The title compound was prepared from  
18    [4-Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-phenyl-  
19    alanine-N-methylamide (400mg, 1.16mmol) by the method  
20    described in example 1f, substituting thiophenethiol in  
21    the place of thiophenol to give a material (320mg,  
22    0.73mmol, 63%) with the following characteristics.

23

24    m.p. 184-186°C

25

26    delta<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO) 8.29 (1H, d, J= 8.1Hz, CONH),  
27    7.84 (1H, m, CONHMe), 7.57 (1H, d, J= 5.1Hz,  
28    Thiophene H), 5H, m, Aromatic H), 7.00 (2H, m,  
29    Thiophene H), 4.50 (1H, m, CHCH<sub>2</sub>Ph), 2.91 (1H, m,  
30    CHCH<sub>2</sub>Ph), 2.75 (1H, m, CHCH<sub>2</sub>Ph), 2.56 (3H, d, J=  
31    4.0Hz, CONHCH<sub>3</sub>), 2.34 (3H, m), 1.99 (1H, d, J= 9.3Hz,

32

33

1    CH<sub>2</sub>SHet),    1.42    (1H,    m,    CHCH<sub>2</sub>CH),    1.29    (1H,    b<sup>m</sup>,  
2    CH(CH<sub>3</sub>)<sub>2</sub>),    0.87    (1H,    m,    CHCH<sub>2</sub>CH),    0.79    (3H,    d,    J=  
3    6.4Hz,    CH(CH<sub>3</sub>)<sub>2</sub>),    and 0.72    (3H,    d,    J= 6.4Hz,    CH(CH<sub>3</sub>)<sub>2</sub>).  
4

5    b) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthio-  
6    methyl)succinyl]-L-phenylalanine-N-methylamide  
7

8    Prepared by the method described in example 1g to  
9    give material with the following characteristics  
10

11    m.p. 236-238°C  
12

13    Analysis calculated for C<sub>23</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>

14    Requires C 57.84 H 6.54 N 8.80

15    Found    C 57.64 H 6.48 N 8.85  
16

17    delta<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO) 8.80 (1H, s, CONHOH), 8.08  
18    (1H, d, J=8Hz, CONH), 7.52 (1H, m, CONHMe), 7.32 (1H,  
19    dd, J= 4.6,2.9Hz, Thiophene H), 7.17 - 6.95 (5H, m,  
20    Aromatic H), 6.89 (2H, m, Thiophene H), 4.46 (1H,  
21    m, CHCH<sub>2</sub>Ph), 2.89 (1H, dd, J=13.6,4.4Hz, CHCH<sub>2</sub>Ph), 2.72  
22    (1H, dd, J= 13.6,10.5Hz, CHCH<sub>2</sub>Ph), 2.54 (3H, d, J=  
23    4.3Hz, CONHCH<sub>3</sub>), 2.46 (1H, d, J= 12.1Hz, CH<sub>2</sub>S), 2.35  
24    (1H, bt, J= 10.2Hz), 2.14 (1H, bt, J= 10.2Hz), 1.98  
25    (1H, dd, J=12.7,2.5Hz, CHCH<sub>2</sub>Ph), 1.35 (1H, bt, J=  
26    11.4Hz, CHCH<sub>2</sub>CH), 1.22 (1H, b<sup>m</sup>, CH(CH<sub>3</sub>)<sub>2</sub>), 0.86 (1H,  
27    bt, J=12.6Hz, CHCH<sub>2</sub>CH), 0.74 (3H, d, J= 6.3Hz,  
28    CH(CH<sub>3</sub>)<sub>2</sub>), and 0.68 (3H, d, J= 6.4Hz, CH(CH<sub>3</sub>)<sub>2</sub>).  
29

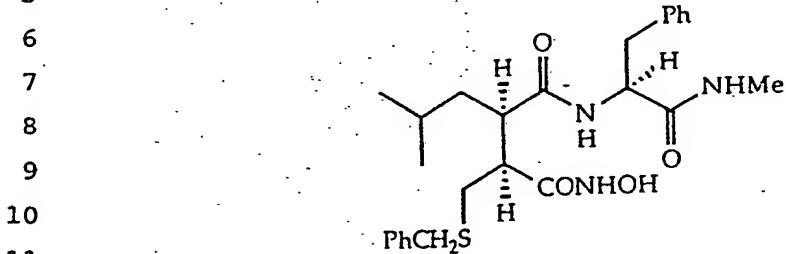
30    delta<sub>C</sub> (63.9MHz, D<sub>6</sub>-DMSO) 172.5, 171.6, 166.1, 138.0,  
31    133.8, 132.7, 129.4, 129.2, 128.1, 127.8, 126.5, 54.2,  
32    46.2, 46.0, 38.5, 37.6, 25.8, 25.2, 24.2, and 21.7.  
33

1    Example 3

2

3    [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzylthiomethyl)  
4    succinyl]-L-phenylalanine-N-methylamide

5



10

11

12

13    Prepared by the method described in example 1g to  
14    give material with the following characteristics

15

16    m.p.      °

17

18    Analysis calculated for C<sub>27</sub>H<sub>37</sub>N<sub>3</sub>O<sub>5</sub>S.0.5H<sub>2</sub>O

19    Requires C 61.81 H 7.30 N 8.00

20    Found     C 61.85 H 7.15 N 7.45

21

22    delta<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO) 8.40 (1H, s, CONHOH), 8.22  
23    (1H, m, NHMe), 7.20 (5H, m, Aromatic H), 6.58 (4H, m),  
24    4.10 (1H, m, CHCH<sub>2</sub>Ph), 3.22 (3H, s, OCH<sub>3</sub>), 3.04 - 2.45  
25    (4H, m, 2xCH<sub>2</sub>Ar), 2.42 (3H, d, J = 6Hz, NHCH<sub>3</sub>), 2.32 -  
26    2.08 (4H, m), 0.78 (2H, m, CHCH<sub>2</sub>CH), and 0.40 - 0.18  
27    (7H, m, (CH<sub>3</sub>)<sub>2</sub>CH).

28

29

30

31

32

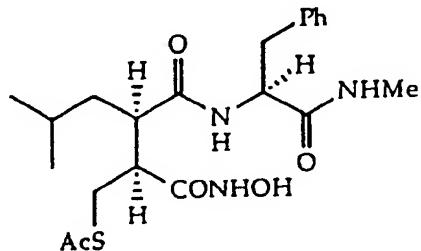
33

1    Example 4

2

3    [ 4 - (N-Hydroxyamino) -2R-isobutyl-3S-(acetylthiomethyl)  
4    succinyl ] -L-phenylalanine-N-methylamide

5



6

7

8

9

10

11

12

13    Prepared by the method described in example 1g to  
14    give material with the following characteristics

15

16    m.p. 226-227°C

17

18    Analysis calculated for C<sub>21</sub>H<sub>31</sub>N<sub>3</sub>O<sub>5</sub>S.H<sub>2</sub>O

19    Requires C 55.37 H 7.30 N 9.22

20    Found    C 55.57 H 6.99 N 9.53

21

22    delta<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO) 8.84 (1H, s, NHOH), 8.36 (1H,  
23    d, J= 8Hz, CONH), 7.80 (1H, d, J= 6Hz, NHMe), 7.20 (%h,  
24    m, Aromatic H), 4.58 (1H, m, CHCH<sub>2</sub>Ph), 3.16 - 2.62  
25    (2H, m, CHCH<sub>2</sub>Ph), 2.54 (3H, d, J= 4Hz, NHCH<sub>3</sub>), 2.22  
26    (3H, s, CH<sub>3</sub>COS), 2.36 - 2.10 (4H, m, CHCHCH<sub>2</sub>S), 1.36  
27    (2H, m, CHCH<sub>2</sub>CH), and 0.98 - 0.66 (7H, m, CH(CH<sub>3</sub>)<sub>2</sub>).

28

29

30

31

32

33

1    Example 5

2

3    [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiomethyl)  
4    succinyl]-L-phenylalanine-N-methylamide

5

6

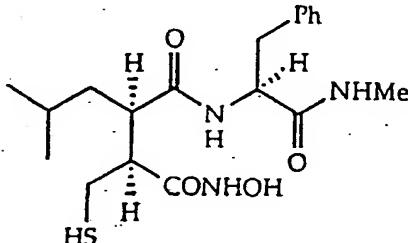
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10

11



12    [4-(N-Hydroxyamino)-2R-isobutyl-3S-(acetylthiomethyl)  
 13    succinyl]-L-phenylalanine-N-methylamide (30mg,  
 14    0.06mmol) was stirred in methanol (3ml) with  
 15    methylamine (1ml methanolic solution) at room  
 16    temperature. After 30 minutes the crystalline  
 17    product (20mg, 0.05mmol, 74%) was filtered off and  
 18    dried.

19

20    m.p. 234°C

21    Analysis calculated for C<sub>19</sub>H<sub>39</sub>N<sub>3</sub>O<sub>4</sub>S·1.5H<sub>2</sub>O

22    Requires C 54.10 H 7.63 N 9.94 S 7.60

23    Found    C 54.28 H 7.16 N 10.43 S 7.80

24

25     $\delta_H$  (250MHz, D<sub>6</sub>-DMSO) 8.28 (1H, d, J= 9Hz, NH<sub>2</sub>),  
 26    7.80 (1H, m, NHMe), 7.22 (5H, m, Aromatic H), 4.60 (1H,  
 27    m, CHCH<sub>2</sub>Ph), 3.08 - 2.56 (2H, m, CHCH<sub>2</sub>Ph), 2.50 (3H, d,  
 28    J= 4Hz, NHCH<sub>3</sub>), 2.40 - 2.02 (4H, m, CHCHCH<sub>2</sub>SH), 1.44  
 29    - 1.22 (2H, m, CHCH<sub>2</sub>CH) and 0.98 - 0.72 (7H, m,  
 30    CH(CH<sub>3</sub>)<sub>2</sub>).

31

32

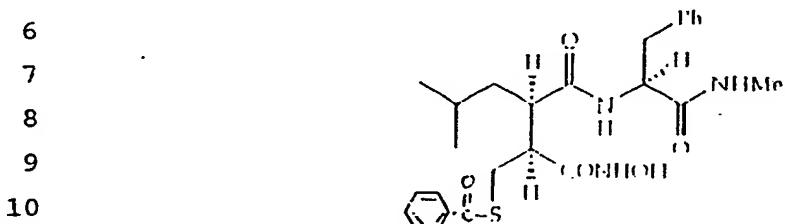
33

1    Example 6

2

3    [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzoylthiomethyl)-  
4    succinyl]-L-phenylalanine-N-methylamide

5



The title compound was prepared by the method described  
in Example 1g to give material with the following  
characteristics

m.p. 227 - 228°

Analysis calculated for C<sub>21</sub>H<sub>31</sub>N<sub>3</sub>O<sub>5</sub>S

Requires C 62.50 H 6.66 N 8.41

Found      C 62.32 H 6.67 N 8.40

delta<sub>H</sub> (250 MHz, CDCl<sub>3</sub>:D<sub>6</sub>DMSO (1:1)) 8.82 (1H, s,  
NHOH), 8.25 (1H, d, J=8.4Hz, NHOH), 7.87 (2H, dd,  
J=8.5, 1.1Hz), 7.60 (2H, m, Ar-H and CONH), 7.50 (2H,  
t, J=8.2Hz), 7.28 (2H, d, J=8.4Hz), 7.16 (2H, t,  
J=7.2Hz), 7.04 (1H, t, J=8.5Hz), 4.65 (1H, m, CHCH<sub>2</sub>Ph),  
3.06 (1H, dd, J=14.1, 5.0Hz, CHCH<sub>2</sub>Ph), 2.90 (1H, dd,  
J=13.9, 10Hz, CHCH<sub>2</sub>Ph), 2.73 (2H, m SCH<sub>2</sub>Ph), 2.65 (3H,  
d, J=4.7Hz, NHMe), 2.33 (1H, dt, J=11.0, 4.7Hz), 1.51  
(1H, t, J=7Hz, CH<sub>2</sub>CHMe<sub>2</sub>), 1.24 (1H, m, CHMe<sub>2</sub>), 0.97  
(1H, t, J=7Hz, CH<sub>2</sub>CHMe<sub>2</sub>), 0.84 (3H, d, J=6.5Hz, CHMe<sub>2</sub>)  
and 0.79 (3H, d; J=6.5Hz, CHMe<sub>2</sub>).

1    Example 7

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(pivaloylthiomethyl)  
4 succinyl]-L-phenylalanine-N-methylamide

5

6

7

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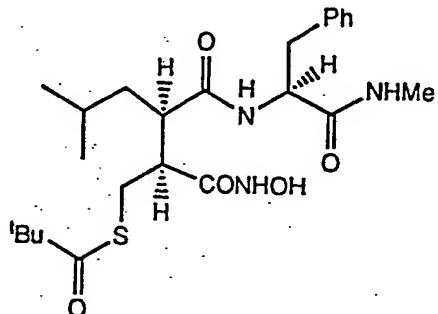
13

14

15 [4-Hydroxy-2R-isobutyl-3S-(pivaloylthiomethyl)  
16 succinyl]-L-phenylalanine-N-methylamide (0.8g, 1.7  
17 mmol) and HOBT (0.31g, 2.1 mmol) were dissolved in 1:1  
18 DCM/DMF and the mixture cooled to 0°C before adding  
19 WSDCI (0.4g, 2.1mmol) and NMM (0.21g, 2.1mmol). The  
20 mixture was stirred at 0°C for 1h to ensure complete  
21 formation of the activated ester. Hydroxylamine  
22 hydrochloride (0.18g, 2.6mmol) and NMM (0.26g, 2.6mmol)  
23 were dissolved in DMF then this mixture was added  
24 dropwise to the cooled solution of the activated ester.  
25 After 1h the reaction was poured into ether/water (1:1)  
26 whereupon the desired product precipitated as white  
27 crystals. These were collected by filtration, further  
28 washed with ether and water, then dried under vacuum at  
29 50°C. This material was recrystallised from  
30 methanol/water (1:1) to remove a trace of the minor  
31 diastereomer (0.38g, 0.7mmol, 45%).

32

33 m.p. 225°C



1 [alpha]<sub>D</sub> = -3.5° (c=2, methanol)

2

3 Analysis calculated for C<sub>24</sub>H<sub>39</sub>N<sub>3</sub>O<sub>5</sub>S.0.5 H<sub>2</sub>O

4 Requires: C58.99 H7.84 N8.60

5 Found: C58.96 H7.63 N8.55

6

7 delta<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO) 8.81 (1H, s, J = 1.5Hz, NHOH),  
8 8.30 (1H, d, J=8Hz, CONH), 7.78 (1H, d, J=6Hz, CONHMe),  
9 7.27-7.03 (5H, m, aromatic H), 4.54 (1H, m, CHCH<sub>2</sub>Ph),  
10 2.94 (1H, dd, J = 12,5Hz, CHCH<sub>2</sub>Ph), 2.79 (1H, dd, J =  
11 13,10Hz, CHCH<sub>2</sub>Ph) 2.56 (3H, d, J = 4.5Hz, NHCH<sub>3</sub>), 2.44  
12 (2H, m), 2.20 (1H, dd, J = 13,3Hz, CH<sub>2</sub>S), 2.07 (1H,  
13 dt), 1.36 (2H, m), 1.13 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 0.87 (1H, m,  
14 CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.79 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and 0.74  
15 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

16

17 delta<sub>C</sub> (63.9MHz, D<sub>6</sub>-DMSO) 172.55, 171.59, 168.24,  
18 138.03, 129.18, 128.00, 126.24, 54.21, 46.48, 45.84,  
19 45.55, 37.61, 28.30, 27.13, 25.64, 25.25, 24.24, and  
20 21.63.

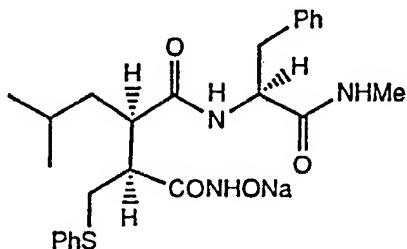
21

22 Example 8

23

24 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)  
25 succinyl]-L-phenylalanine-N-methylamide sodium salt

26



1 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)  
 2 succinyl]-L-phenylalanine-N-methylamide (0.2g, 0.4  
 3 mmol) was dissolved in 20ml of methanol and 1eq of 0.1N  
 4 NaOH(aq) added. The solvent was removed in vacuo and  
 5 the residue dissolved in water and freeze-dried  
 6 (0.21g, 0.4 mmol, 100%).

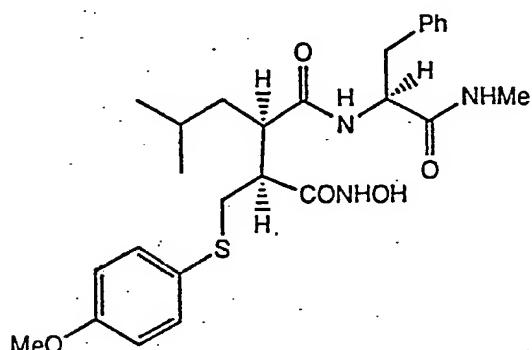
7 m.p. 184°C  
 8

9 [alpha]<sub>D</sub> = -7.7° (c=2, methanol)  
 10

11 delta<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO) 8.62 (1H, s, J = 1.5Hz, NHOH),  
 12 8.28 (1H, d, J = 8Hz, CONH), 7.26 - 7.04 (10H, m,  
 13 aromatic H), 4.43 (1H, m, CHCH<sub>2</sub>Ph), 3.00 (1H, dd, J =  
 14 14,4Hz, CHCH<sub>2</sub>Ph), 2.84 (1H, dd, J = 14,10Hz, CHCH<sub>2</sub>Ph),  
 15 2.55 (3H, d, J = 4.5Hz, NHCH<sub>3</sub>), 2.46 (3H, m), 2.21 (1H,  
 16 m), 1.39 (1H, m), 1.14 (1H, m), 1.00 (1H, m), and 0.70  
 17 (6H, d, J = 5.7Hz)  
 18

19 Example 9  
 20

21 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenyl-  
 22 thiomethyl)]



1 succinyl]-L-phenylalanine-N-methylamide[4-Hydroxy-2R-  
2 isobutyl-3S-(4-methoxyphenylthiomethyl)succinyl]-L-  
3 phenylalanine-N-methylamide (0,5g, 1 mmol) and HOBT  
4 (0.18g, 1.2 mmol) were dissolved in 1:1 DCM/DMF and the  
5 mixture cooled to 0°C before adding WSDCI (0.23g,  
6 1.2mmol) and NMM (0.12g, 1.2mmol). The mixture was  
7 stirred at 0°C for 1h to ensure complete formation of  
8 the activated ester. Hydroxylamine hydrochloride (0.1g,  
9 1.5mmol) and NMM (0.15g, 1.5mmol) were dissolved in DMF  
10 then this mixture was added dropwise to the cooled  
11 solution of the activated ester. After 1h the reaction  
12 was poured into ether/water (1:1) whereupon the desired  
13 product precipitated as white crystals. These were  
14 collected by filtration, further washed with ether and  
15 water, then dried under vacuum at 50°C. This material  
16 was recrystallised from methanol/water (1:1) to remove  
17 a trace of the minor diastereomer (0.36g, 0.7mmol,  
18 72%).

19 m.p. 225°C  
20

21 [alpha]<sub>D</sub> = +8° (c=0.5, methanol)  
22

23 Analysis calculated for C<sub>26</sub>H<sub>35</sub>N<sub>3</sub>O<sub>5</sub>S  
24 Requires: C62.25 H7.04 N8.38  
25 Found: C62.43 H7.09 N8.37  
26

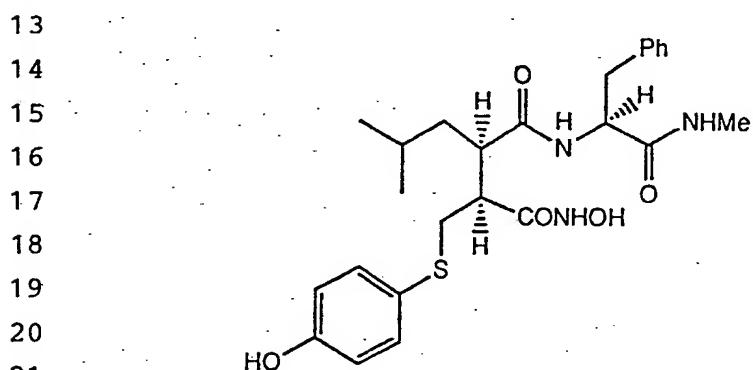
27 delta<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO) 8.83 (1H, s, J = 1.5Hz, NHOH),  
28 8.28 (1H, d, J = 8Hz, CONH), 7.83 (1H, d, J = 6Hz,  
29 CONHMe), 7.28 - 6.86 (9H, m, aromatic H), 4.52 (1H, m,  
30 CHCH<sub>2</sub>Ph), 3.73 (3H, s, OCH<sub>3</sub>), 2.91 (1H, dd, J = 14,4Hz,  
31 CHCH<sub>2</sub>Ph), 2.75 (1H, dd, J = 14,10Hz, CHCH<sub>2</sub>Ph), 2.57  
32 (3H, d, J = 4.5Hz, NHCH<sub>3</sub>), 2.50 - 2.34 (2H,m), 2.16 -  
33

1 1.99 (2H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>) 1.36 (2H, m), 0.88 (1H, m,  
2 CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.80 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and 0.73  
3 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

4  
5 delta<sub>C</sub> (63.9MHz, D<sub>6</sub>-DMSO) 172.79, 171.62, 168.39,  
6 138.14, 131.34, 129.19, 128.00, 126.44, 114.59, 55.32,  
7 54.20, 38.68, 25.63, 25.17, 24.26, and 21.70.

8  
9 Example 10

10  
11 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-  
12 thiomethyl) succinyl]-L-phenylalanine-N-methylamide



1 whereupon the desired product precipitated as white  
2 crystals. These were collected by filtration, further  
3 washed with ether and water, then dried under vacuum at  
4 50°C. This material was recrystallised from  
5 methanol/water (1:1) to remove a trace of the minor  
6 diastereomer (0.13g, 0.2mmol, 31%).

7

8 m.p. 216°C

9

10  $[\alpha]_D = -65^\circ$  (c=0.5, methanol)

11

12 Analysis calculated for C<sub>25</sub>H<sub>33</sub>N<sub>3</sub>O<sub>5</sub>S

13 Requires: C61.58 H6.82 N8.62

14 Found: C61.43 H6.81 N8.08

15

16  $\delta_H$  (250MHz, D<sub>6</sub>-DMSO) 8.82 (1H, s, J = 1.5Hz, NHOH),  
17 8.26 (1H, d, J = 8Hz, CONH), 7.81 (1H, d, J = 6Hz,  
18 CONHMe), 7.27 - 6.64 (9H, m, aromatic H), 4.49 (1H, m,  
19 CHCH<sub>2</sub>Ph), 2.90 (1H, dd, J=14,4Hz, CHCH<sub>2</sub>Ph), 2.74 (1H,  
20 dd, J=14,10Hz, CHCH<sub>2</sub>Ph), 2.57 (3H, d, J = 4.5Hz,  
21 NHCH<sub>3</sub>), 2.54 - 2.29 (2H, m), 2.14 - 1.98 (2H, m,  
22 CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.35 (2H, m), 0.88 (1H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>),  
23 0.80 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and 0.73 (3H, d, J =  
24 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

25

26  $\delta_C$  (63.9MHz, D<sub>6</sub>-DMSO) 172.81, 171.66, 168.46,  
27 156.50, 133.02, 132.17, 129.17, 128.02, 126.44, 124.17,  
28 116.00, 54.20, 46.35, 46.13, 37.59, 35.40, 25.62,  
29 25.16, 24.27, and 21.69.

30

31

32

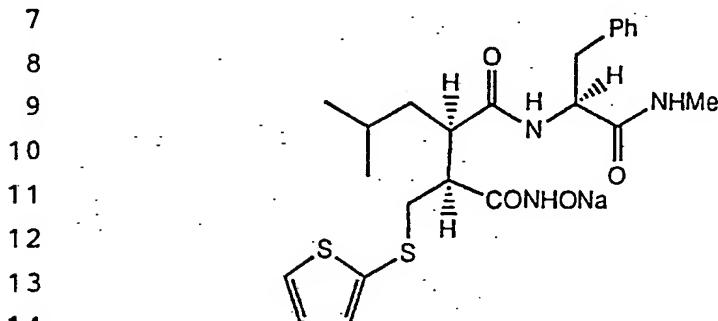
33

1    Example 11

2

3    [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thiophenethio-  
4    methyl)succinyl]-L-phenylalanine-N-methylamide sodium  
5    salt

6



16    [4-Hydroxyamino)-2R-isobutyl-3S-(2-thiophenethiomethyl)  
17    succinyl]-L-phenylalanine-N-methylamide (0.2g, 0.4  
18    mmol) was dissolved in 20ml of methanol and 1eq of 0.1N  
19    NaOH(aq) added. The solvent was removed in vacuo and  
20    the residue dissolved in water and freeze-dried  
21    (0.21g, 0.4 mmol, 100%).

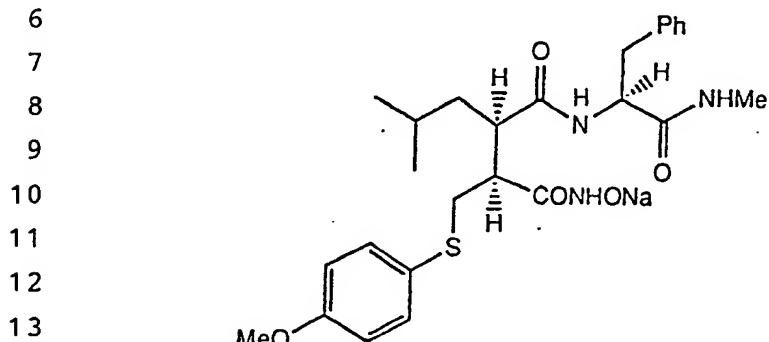
22    m.p. 170°C

23     $[\alpha]_D = -67^\circ$  (c=1, methanol)

24     $\delta_H$  (250MHz,  $d_6$ -DMSO), 7.51 (1H, d), 7.19 - 6.97  
25    (8H, m, aromatic H), 4.32 (1H, m,  $\underline{CHCH}_2\text{Ph}$ ), 3.00 (1H,  
26    dd, J = 14,4Hz,  $\underline{CHCH}_2\text{Ph}$ ), 2.84 (1H, dd, J = 14,10Hz,  
27     $\underline{CHCH}_2\text{Ph}$ ) 2.53 (3H, d, J = 4.5Hz,  $\underline{NHCH}_3$ ), 2.46 2.19 (3H,  
28    m), 1.37 (1H, m), 1.09 (1H, m), 0.93 (1H, m), and 0.67  
29    (6H, m)

1   Example 12

2  
3   [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenyl-  
4   thiomethyl)succinyl]-L-phenylalanine-N-methylamide  
5   sodium salt



16  
17   [4-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenylthio-  
18   methyl)succinyl]-L-phenylalanine-N-methylamide (0,1g,  
19   0.2 mmol) was dissolved in 20ml of methanol and 1eq of  
20   0.1N NaOH(aq) added. The solvent was removed in vacuo  
21   and the residue dissolved in water and freeze-dried  
22   (0.1g, 0.2 mmol, 100%).

23  
24   m.p. 174°C

25  
26   [alpha]D = -58° (c=1, methanol)

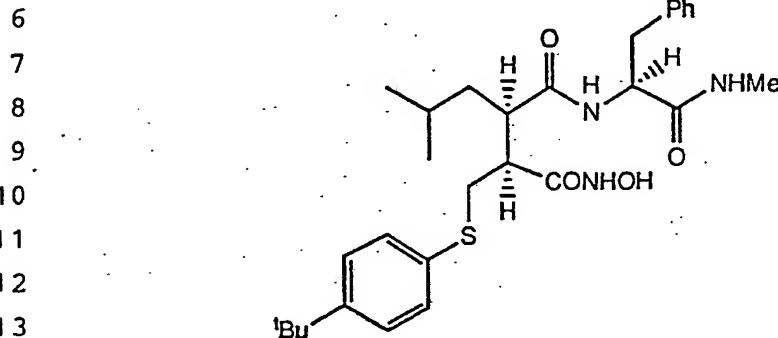
27  
28   deltaH (250MHz, D6-DMSO) 7.26 - 7.04 (10H, m, aromatic  
29   H), 4.31 (1H, m, CHCH2Ph), 3.73 (3H, s, OCH3), 3.25 -  
30   2.72 (2H, m, CHCH2Ph), 2.50 (3H, s, NHCH3), 2.36 (1H,  
31   m), 2.15 (1H, m), 1.37 (1H, m), 0.95 (1H, m), and 0.69  
32   (6H, d, CHCH2(CH3)2).

1   Example 13

2

3   [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-tertbutylphenyl-  
4   thiomethyl) succinyl]-L-phenylalanine-N-methylamide

5



16   [4-Hydroxy-2R-isobutyl-3S-(4-tertbutylphenylthiomethyl)  
17   succinyl]-L-phenylalanine-N-methylamide (5.0g, 10 mmol)  
18   and HOBT (1.76g, 12 mmol) were dissolved in 1:1 DCM/DMF  
19   and the mixture cooled to 0°C before adding WSDCI  
20   (2.3g, 12mmol) and NMM (1.2g, 12mmol). The mixture was  
21   stirred at 0°C for 1h to ensure complete formation of  
22   the activated ester. Hydroxylamine hydrochloride  
23   (1.0g, 15mmol) and NMM (1.2g, 15mmol) were dissolved in  
24   DMF then this mixture was added dropwise to the cooled  
25   solution of the activated ester. After 1h the reaction  
26   was poured into ether/water (1:1) whereupon the desired  
27   product precipitated as white crystals. These were  
28   collected by filtration, further washed with ether and  
29   water, then dried under vacuum at 50°C. This material  
30   was repeatedly recrystallised from methanol/water (1:1)  
31   to remove a trace of the minor diastereomer (0.7g,  
32   1.3mmol, 14%).

1 M.p. 188.5 -190°C

2

3 Analysis calculated for C<sub>29</sub>H<sub>41</sub>N<sub>3</sub>O<sub>4</sub>S

4 Requires: C66.00 H7.83 N7.96

5 Found: C65.80 H7.81 N7.76

6

7   delta<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO) 8.83 (1H, s, NHOH), 8.33 (1H,  
 8   d, J = 8Hz, CONH), 7.86 (1H, d, J = 6Hz, CONHMe), 7.28  
 9   - 6.90 (9H, m, aromatic H), 4.60 (1H, m, CHCH<sub>2</sub>Ph), 2.94  
 10 (1H, dd, J = 14,4Hz, CHCH<sub>2</sub>Ph), 2.77 (1H, dd, J =  
 11 14,10Hz, CHCH<sub>2</sub>Ph), 2.58 (3H, d, J = 4.5Hz, NHCH<sub>3</sub>), 2.55  
 12 - 2.37 (2H, m), 2.22 - 2.08 (2H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.37  
 13 (2H, m), 1.26 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 0.88 (1H, m,  
 14 CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.81 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and 0.74  
 15 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

16

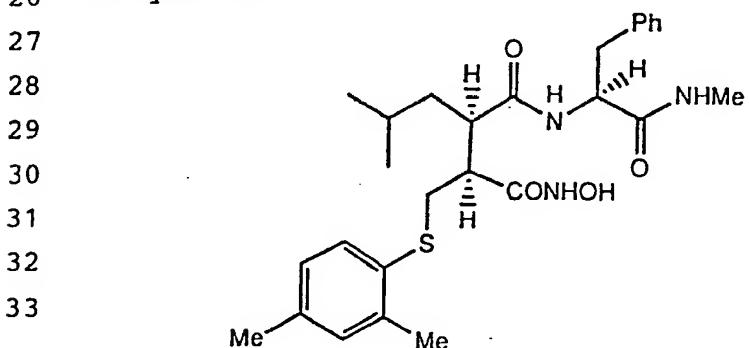
17   delta<sub>C</sub> (63.9MHz, D<sub>6</sub>-DMSO) 172.88, 171.59, 168.34,  
 18   147.87, 138.10, 133.09, 129.13, 127.95, 127.45, 126.36,  
 19   125.70, 54.19, 54.20, 46.38, 46.06, 37.70, 34.20, 32.79  
 20   31.24, 25.64, 25.19, 24.25, and 21.72.

21

### 22 Example 14

23

24 [ 4 - ( N - Hydroxyamino ) - 2 R - isobutyl - 3 S - ( 2 , 4 -  
25 dimethylphenylthiomethyl ) succinyl ] - L - phenylalanine - N -  
26 methylamide



1 [4-Hydroxy-2R-isobutyl-3S-(2,4-dimethylphenylthio-  
2 methyl)succinyl]-L-phenylalanine-N-methylamide (1.8g,  
3 3.7 mmol) and HOBT (0.67g, 12 mmol) were dissolved in  
4 1:1 DCM/DMF and the mixture cooled to 0°C before adding  
5 WSCl (0.86g, 4.5mmol) and NMM (0.45g, 4.5mmol). The  
6 mixture was stirred at 0°C for 1h to ensure complete  
7 formation of the activated ester. Hydroxylamine  
8 hydrochloride (0.39g, 5.6mmol) and NMM (0.56g, 5.6mmol)  
9 were dissolved in DMF then this mixture was added  
10 dropwise to the cooled solution of the activated ester.  
11 After 1h the reaction was poured into ether/water (1:1)  
12 whereupon the desired product precipitated as white  
13 crystals. These were collected by filtration, further  
14 washed with ether and water, then dried under vacuum at  
15 50°C. This material was repeatedly recrystallised from  
16 methanol/water (1:1) to remove a trace of the minor  
17 diastereomer (1.08g, 2.2mmol, 58%).  
18

19 m.p. 226°C (dec.)  
20

21 Analysis calculated for C<sub>27</sub>H<sub>37</sub>N<sub>3</sub>O<sub>4</sub>S

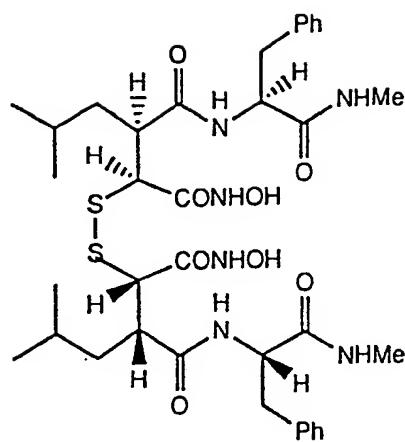
22 Requires: C64.90 H7.46 N8.41

23 Found: C65.15 H7.48 N8.40  
24

25 δ<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO) 8.83 (1H, s, NHOH), 8.32 (1H,  
26 d, J = 8Hz, CONH), 7.85 (1H, d, J = 6Hz, CONHMe), 7.30  
27 - 6.71 (9H, m, aromatic H), 4.56 (1H, m, CHCH<sub>2</sub>Ph), 2.91  
28 (1H, dd, J = 14,4Hz, CHCH<sub>2</sub>Ph), 2.76 (1H, dd, J =  
29 14,10Hz, CHCH<sub>2</sub>Ph), 2.57 (3H, d, J = 4.5Hz, NHCH<sub>3</sub>), 2.53  
30 - 2.38 (2H, m), 2.23 (3H, s, C<sub>6</sub>H<sub>5</sub>(CH<sub>3</sub>)<sub>2</sub>), 2.13 (3H, s,  
31 C<sub>6</sub>H<sub>5</sub>(CH<sub>3</sub>), 1.30 (2H, m), 0.89 (1H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>),  
32 0.81 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and 0.74 (3H, d, J =  
33 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

1      Example 15

2



13    [4-(N-Hydroxyamino)-2R-isobutyl-3S-(acetylthiomethyl)  
 14    succinyl]-L-phenylalanine-N-methylamide (1.0g, 2.4  
 15    mmol) was dissolved in 750ml methanol and 350ml pH 7  
 16    buffer added. Left to stand overnight and solvent  
 17    removed in vacuo to 2/3 volume, left to crystallise for  
 18    a further two hours. Filtered and dried to give 0.87g  
 19    off-white crystals

20

21    Analysis calculated for C<sub>38</sub>H<sub>56</sub>N<sub>6</sub>O<sub>8</sub>S<sub>2</sub>.1.9H<sub>2</sub>O  
 22    Requires: C55.34 H6.93 N9.88  
 23    Found:    C55.44 H7.32 N10.21

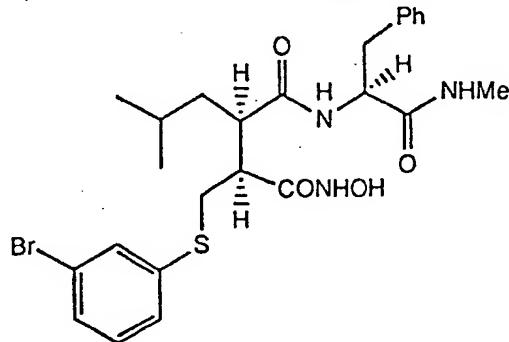
24

25    Example 16

26

27    [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-bromophenyl-  
 28    thiomethyl) succinyl]-L-phenylalanine-N-methylamide

29



1 Prepared by the method described in example 1g to give  
2 material with the following characteristics.  
3

4 m.p. 225 - 229°C  
5

6  $[\alpha]_D = -164.8^\circ$   
7

8 Analysis calculated for  $C_{25}H_{32}BrN_3O_4S$   
9 Requires: C54.40 H5.89 N7.40

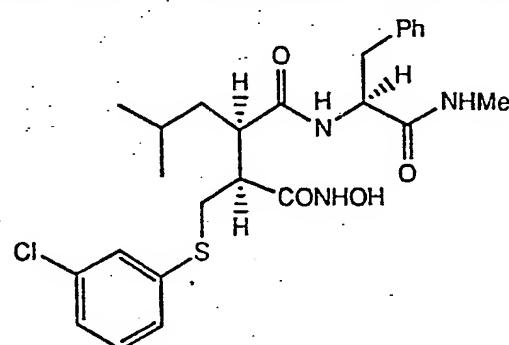
10 Found: C54.54 H5.86 N7.63  
11

12  $\delta_H$  (250MHz,  $D_6$ -DMSO) 8.83 (1H, s,  $NHOH$ ), 8.35 (1H,  
13 d,  $J = 8Hz$ ,  $CONH$ ), 7.90 (1H, q,  $J = 6Hz$ ,  $CONHMe$ ), 7.35  
14 - 6.87 (9H, m, aromatic H), 4.64 (1H, m,  $CHCH_2Ph$ ), 2.94  
15 (1H, dd,  $J = 14, 4Hz$ ,  $CHCH_2Ph$ ), 2.76 (1H, t,  $J = 13Hz$ ,  
16  $CHCH_2Ph$ ) 2.60 (3H, d,  $J = 5Hz$ ,  $NHCH_3$ ), 2.55 - 2.35 (2H,  
17 m,  $CH_2S$ ), 2.15 (1H, t,  $J = 10Hz$ ,  $CHCO$ ), 2.01 (1H, d,  $J$   
18 = 11.5Hz,  $CHCO$ ), 1.37 (2H, m), 0.88 (1H, m,  
19  $CH_2CH(CH_3)_2$ ), 0.81 (3H, d,  $J = 6Hz$ ,  $CH(CH_3)_2$ ), and 0.74  
20 (3H, d,  $J = 6Hz$ ,  $CH(CH_3)_2$ ).  
21

22  $\delta_C$  (63.9MHz,  $D_6$ -DMSO) 173.0, 171.0, 168.8, 139.8,  
23 138.0, 130.5, 129.0, 128.5, 127.5, 125.8, 125.5, 54.2,  
24 46.0, 45.5, 38.0, 31.5, 25.5, 25.2, 24.7, and 21.0.  
25

26 Example 17  
27

28 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-chlorophenylthio-  
29 methyl) succinyl]-L-phenylalanine-N-methylamide  
30



1 Prepared by the method described in example 1g to give  
2 material with the following characteristics.

3

4 m.p. 231-234°C

5

6  $[\alpha]_D = -96.5^\circ$

7

8 Analysis calculated for  $C_2^5H_3^2ClN_3O_4S$

9 Requires: C59.34 H6.37 N8.30

10 Found: C59.51 H6.43 N8.24

11

12  $\delta_H$  (250MHz,  $D_6$ -DMSO) 8.85 (1H, s, NH<sub>2</sub>OH), 8.37 (1H,  
13 d, J = 8.5Hz, CONH), 7.90 (1H, m, CONHMe), 7.30 - 6.88  
14 (9H, m, aromatic H), 4.66 (1H, m, CHCH<sub>2</sub>Ph), 2.96 (1H,  
15 bd, J = 14Hz, CHCH<sub>2</sub>Ph), 2.76 (1H, bt, J = 13Hz,  
16 CHCH<sub>2</sub>Ph) 2.60 (3H, d, J = 5Hz, NHCH<sub>3</sub>), 2.55 - 2.40 (2H,  
17 m, CH<sub>2</sub>S), 2.16 (1H, m, CHCO), 2.01 (1H, d, J = 14Hz,  
18 CHCO), 1.37 (2H, m), 0.91 (1H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.81  
19 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and 0.74 (3H, d, J =  
20 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

21

22  $\delta_C$  (63.9MHz,  $D_6$ -DMSO) 172.7, 171.6, 168.1, 139.2,  
23 138.1, 130.3, 129.2, 127.9, 126.2, 125.9, 125.5, 125.0,  
24 54.1, 46.3, 45.8, 37.8, 32.0, 25.7, 25.2, 24.2, and  
25 21.7.

26

27

28

29

30

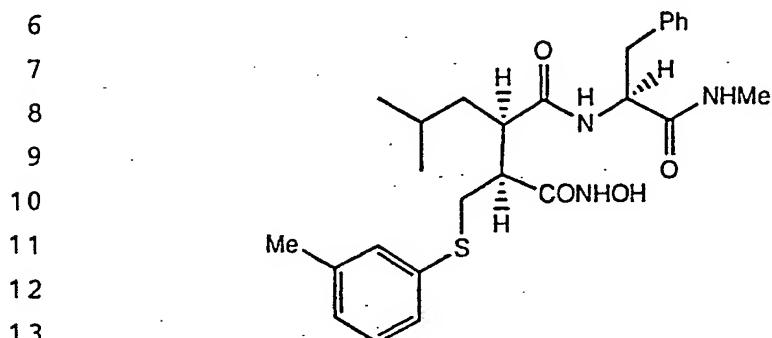
31

32

33

1    Example 18

2  
3 [ 4 - ( N - H y d r o x y a m i n o ) - 2 R - i s o b u t y l - 3 S - ( 3 -  
4    m e t h y l p h e n y l t h i o m e t h y l ) s u c c i n y l ] - L - p h e n y l a l a n i n e - N -  
5    m e t h y l a m i d e



15    Prepared by the method described in example 1g to give  
16    material with the following characteristics.

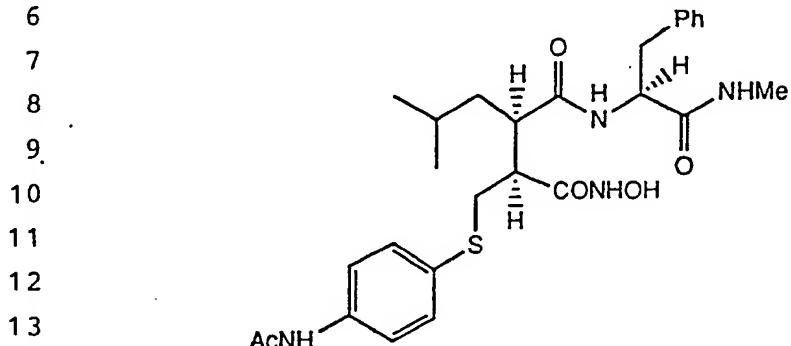
17  
18    Analysis calculated for C<sub>26</sub>H<sub>35</sub>N<sub>3</sub>O<sub>4</sub>S  
19    Requires: C64.30 H7.26 N8.65  
20    Found:    C63.81 H7.21 N8.48

21  
22    delta<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO) 8.83 (1H, s, NH<sub>OH</sub>), 8.35 (1H,  
23    d, J = 8.5Hz, CONH), 7.86 (1H, m, CONHMe), 7.28 - 6.77  
24    (9H, m, aromatic H), 4.66 (1H, m, CHCH<sub>2</sub>Ph), 2.96 (1H,  
25    dd, J = 14,4Hz, CHCH<sub>2</sub>Ph), 2.80 (1H, bt, J = 13Hz,  
26    CHCH<sub>2</sub>Ph) 2.59 (3H, d, J = 5Hz, NHCH<sub>3</sub>), 2.55 - 2.37 (2H,  
27    m, CH<sub>2</sub>S), 2.16 (2H, m, 2xCHCO), 1.38 (2H, m), 0.91 (1H,  
28    m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.81 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and  
29    0.74 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>).  
30  
31  
32  
33

1   Example 19

2

3   [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-  
 4   aminophenylthiomethyl)succinyl]-L-phenylalanine-N-  
 5   methylamide.



16   A) [2R-isobutyl-3S-(4-aminophenylthiomethyl)succinyl]-  
 17   L-phenylalanine -N-methylamide.

18

19   Prepared by the method described in example 1f to give  
 20   material with the following characteristics.

21

22   delta<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO) 8.27 (1H, d, J = 8.5Hz, CONH),  
 23   7.81 (1H, m, CONHMe), 7.30 - 7.00 (5H, m, phenyl H),  
 24   6.86 (2H, d, J = 8.5Hz, aromatic H), 6.45 (2H, d, J =  
 25   8.5Hz, aromatic H), 5.25 (1H, bs, CO<sub>2</sub>H), 4.48 (1H, m,  
 26   CHCH<sub>2</sub>Ph), 2.91 (1H, dd, J = 14,4Hz, CHCH<sub>2</sub>Ph), 2.88 (1H,  
 27   dd, J = 14,10Hz, CHCH<sub>2</sub>Ph) 2.56 (3H, d, J = 5Hz, NHCH<sub>3</sub>),  
 28   2.43 - 2.24 (3H, m, CH<sub>2</sub>S and CHCO), 2.03 (1H, d, J =  
 29   10Hz, CHCO), 1.41 (1H, t, J = 11Hz, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.26  
 30   (1H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.85 (1H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.81  
 31   (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and 0.74 (3H, d, J=6Hz,  
 32   CH(CH<sub>3</sub>)<sub>2</sub>).

33

1       B) [2R-isobutyl-3S-(4-(N-acetyl)aminophenyl-thio-  
2       methyl)- succinyl]-Lphenylalanine-N-methylamide.

3  
4       The product from above (350mg, 0.74 mmol) was dissolved  
5       in DCM (5 ml) cooled in an ice bath then triethylamine  
6       (75mg, 0.74 mmol), DMAP (91mg, 7.4 mmol) and finally  
7       acetic anhydride (83mg, 8.2 mmol) were added and the  
8       solution stirred at RT for 90 minutes. The mixture was  
9       partitioned between ethyl acetate and citric acid then  
10      the organic layer washed with water and finally dried  
11      over magnesium sulphate. Solvent removal gave the crude  
12      product as pale yellow crystals (160mg, 0.31 mmol,  
13      42%).

14  
15      delta<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO) 9.94 (1H, s, CO<sub>2</sub>H), 8.34 (1H,  
16      d, J = 8.5Hz, CONH), 7.90 (1H, m, CONHMe), 7.46 (2H, d,  
17      J = 8.5Hz, aromatic H) 7.30 - 7.00 (5H, m, phenyl H),  
18      6.96 (2H, d, J = 8.5Hz, aromatic H), 4.57 (1H, m,  
19      CHCH<sub>2</sub>Ph), 2.91 (1H, dd, J = 14,4Hz, CHCH<sub>2</sub>Ph), 2.88 (1H,  
20      bt, J = 13Hz, CHCH<sub>2</sub>Ph), 2.58 (3H, d, J = 5Hz, NHCH<sub>3</sub>),  
21      2.43 - 2.16 (3H, m, CH<sub>2</sub>S and CHCO), 2.10 (1H, d, J =  
22      14Hz, CHCO), 1.35 (1H, t, J = 14Hz, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.26  
23      (1H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.86 (1H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.81  
24      (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and 0.74 (3H, d, J =  
25      6Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

26  
27      C) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-  
28      aminophenylthiomethyl)succinyl]-L-phenylalanine-N-  
29      methylamide.

30  
31      Prepared by the method described in example 1g to give  
32      material with the following characteristics.

33

1 m.p. 201 -202°C (dec.)

2

3  $[\alpha]_D = -7.5^\circ$  (c=1.0, methanol)

4

5  $\delta_H$  (250MHz,  $D_6$ -DMSO) 9.90 (1H, s, NHOH), 8.82 (1H,  
6 s, NHOH), 8.30 (1H, d,  $J = 8.5\text{Hz}$ , CONH), 7.85 (1H, m,  
7 CONHMe), 7.45 (2H, d,  $J = 8.5\text{Hz}$ , aromatic H), 7.28 -  
8 6.94 (5H, m, phenyl H), 6.90 (2H, d,  $J = 8.5\text{Hz}$ ,  
9 aromatic H), 4.66 (1H, m, CHCH<sub>2</sub>Ph), 2.90 (1H, dd,  $J =$   
10 14.4Hz, CHCH<sub>2</sub>Ph), 2.76 (1H, bt,  $J = 13\text{Hz}$ , CHCH<sub>2</sub>Ph),  
11 2.50 (3H, d,  $J = 5\text{Hz}$ , NHCH<sub>3</sub>), 2.49 - 2.35 (2H, m,  
12 CH<sub>2</sub>S), 2.14 (1H, m, CHCO), 2.03 (4H, s + m, COCH<sub>3</sub> and  
13 CHCO), 1.35 (2H, m), 0.86 (1H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.81  
14 (3H, d,  $J = 6\text{Hz}$ , CH(CH<sub>3</sub>)<sub>2</sub>), and 0.74 (3H, d,  $J = 6\text{Hz}$ ,  
15 CH(CH<sub>3</sub>)<sub>2</sub>).

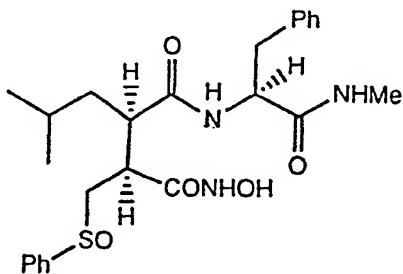
16

17 Example 20

18

19 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfinyl-  
20 methylsuccinyl]-L-phenylalanine-N-methylamide.

21



22

23

24

25

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29

30

31 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylthiomethyl-  
32 succinyl]-L-phenylalanine-N-methylamide (250mg,  
33 0.53mmol) was dissolved in methanol (50 ml) and meta-

1 chloroperbenzoic acid (100mg, 0.58 mmol) was added.  
2 After stirring for 1h at room temperature ether was  
3 added and the mixture filtered. Solvent removal gave  
4 the crude white solid which was recrystallised from  
5 methanol / water then slurried in ether to remove final  
6 traces of meta-chlorobenzoic acid to give the desired  
7 material (70 mg, 0.014 mmol, 27%).

8

9 m.p. 186 -188°C

10

11  $[\alpha]_D = -13.6^\circ$  (c=0.5, methanol)

12

13 Analysis calculated for  $C_{25}H_{33}N_3O_5S \cdot 0.5H_2O$

14 Requires: C60.46 H6.90 N8.46

15 Found: C60.58 H6.69 N8.29

16

17  $\delta_H$  (250MHz,  $D_6$ -DMSO, mixture of diastereomers) 9.04  
18 + 8.93 (1H, 2xs, NHOH), 8.29 + 8.16 (1H, 2xd, J = 8.5  
19 Hz, CONH), 7.79 (1H, m, CONHMe), 7.90 - 7.40 (8H, m,  
20 aromatic H), 7.06 + 6.82 (2H, 2xm, SO-Aromatic), 4.37  
21 (1H, m, CHCH<sub>2</sub>Ph), 2.93 - 2.58 (3H, m, containing  
22 CHCH<sub>2</sub>Ph), 2.52 (3H, m, NHCH<sub>3</sub>), 2.49 + 2.37 (1H, 2xm),  
23 1.49 - 1.25 (2H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub> and CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.95  
24 (1H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.81 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>),  
25 and 0.74 (3H, d, J=6Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

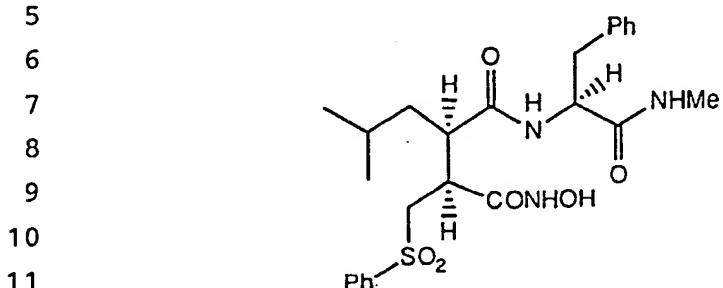
26

27  $\delta_C$  (63.9MHz,  $D_6$ -DMSO, mixture of diastereomers)  
28 172.2, 171.4, 171.3, 167.7, 144.5, 138.0, 137.9, 131.3,  
29 130.9, 129.6, 129.3, 129.1, 128.8, 128.3, 127.8, 126.5,  
30 126.2, 124.3, 123.6, 59.8, 58.1, 54.3, 54.0, 46.2,  
31 45.8, 41.6, 40.9, 37.6, 37.4, 25.6, 25.0, 24.3, 24.2,  
32 21.7, and 21.6.

33

1    Example 21

2

3    [ 4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfonyl-  
4    methylsuccinyl]-L-phenylalanine-N-methylamide.

[ 4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylthiomethyl-succinyl]-L-phenylalanine-N-methylamide (50mg, 0.11mmol) was dissolved in methanol (12 ml) and meta-chloroperbenzoic acid (40mg, 0.23 mmol) was added. After stirring for 3h at room temperature ether was added and the mixture filtered. Solvent removal gave the crude white solid which was slurried in ether to remove final traces of meta-chlorobenzoic acid to give the desired material.

m.p. 228 - 231°C

$[\alpha]_D = 16.8^\circ$  (c=0.5, methanol)

Analysis calculated for  $C_{25}H_{33}N_3O_6S \cdot 0.3H_2O$

Requires: C58.99 H6.65 N8.25

Found:      C58.92 H6.51 N8.05

delta<sub>H</sub>

(250MHz, D<sub>6</sub>-DMSO) 8.66 (1H, s, NH<sub>OH</sub>), 8.25 (1H, d, J = 8.5 Hz, CONH), 7.83 (1H, m, CONHMe), 7.75 - 7.50 (5H, m, aromatic H), 7.30 7.05 (5H, m, aromatic H),

1 4.36 (1H, m,  $\text{CHCH}_2\text{Ph}$ ), 2.86 (1H, dd,  $J = 14,5$  Hz,  
 2  $\text{CHCH}_2\text{Ph}$ ), 2.75 (1H, dd,  $J = 14,10$  Hz,  $\text{CHCH}_2\text{Ph}$ ), 2.54  
 3 (3H, d,  $J = 4.5$  Hz,  $\text{NHCH}_3$ ), 2.54 (2H, m), 1.30 (2H, m,  
 4  $\text{CH}_2\text{CH}(\text{CH}_3)_2$  and  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 0.86 (1H, m,  
 5  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 0.75 (3H, d,  $J = 6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), and 0.71  
 6 (3H, d,  $J = 6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ).

7

8 Example 22

9

10 [4-(N-Hydroxyamino)-2R-isobutyl-3S-  
 11 thiophenylsulphinylmethyl-succinyl]-L-phenylalanine-N-  
 12 methylamide

13

14

15

16

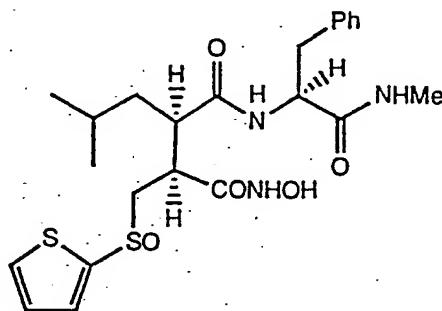
17

18

19

20

21



22

23 [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylthio-  
 24 methyl-succinyl]-L-phenylalanine-N-methylamide (50mg,  
 25 0.11mmol) was treated as described in example 21 to  
 26 yield the title compound (16mg, 0.03 mmol, 29%) as a  
 27 mixture of diastereomer with the following  
 characteristics:

28

29 m.p. 195 -197°C (dec.)

30

31 Analysis calculated for  $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_5\text{S}_2 \cdot 0.5\text{H}_2\text{O}$

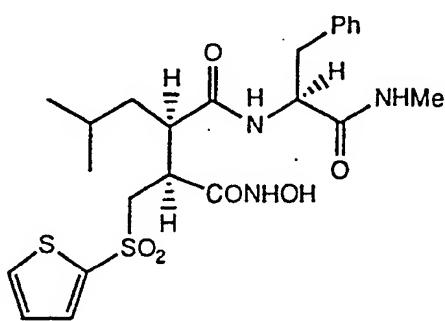
32 Requires: C54.96 H6.42 N8.36

33 Found: C54.91 H6.23 N8.23

1   delta<sub>H</sub> (250MHz, D<sub>6</sub>-DMSO, mixture of diastereomers) 9.04  
2   + 8.96 (1H, 2xs, NH<sub>OH</sub>), 8.34 + 8.29 (1H, 2xd, J = 8.5  
3   Hz, CONH), 8.02 + 7.98 (1H, 2xm, CONHMe), 7.81 (1H, bs,  
4   thiophene-H), 7.42 (1H, s, thiophene-H), 7.25 - 7.15  
5   (5H, m, phenyl), 7.03 (1H, bs, thiophene-H), 4.43 (1H,  
6   m, CHCH<sub>2</sub>Ph), 3.0 - 2.6 (4H, m, containing CHCH<sub>2</sub>Ph),  
7   2.52 (7H, m, containing NHCH<sub>3</sub>), 2.05 (1H, m), 1.6 - 1.2  
8   (2H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub> and CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.87 (1H, m,  
9   CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), and 0.85 - 0.71 (6H, m, CH(CH<sub>3</sub>)<sub>2</sub>).  
10

11   Example 23  
12

13   [ 4 - ( N - H y d r o x y a m i n o ) - 2 R - i s o b u t y l - 3 S -  
14   thiophenylsulphonylmethyl-succinyl ] -L-phenylalanine-N-  
15   methylamide.



25   [ 4 - ( N - H y d r o x y a m i n o ) - 2 R - i s o b u t y l - 3 S - t h i o p h e n y l t h i o -  
26   m e t h y l - s u c c i n y l ] - L - p h e n y l a l a n i n e - N - m e t h y l a m i d e ( 75 m g ,  
27   0.16 mmol ) w a s t r e a t e d a s d e s c r i b e d i n e x a m p l e 22 t o  
28   y i e l d t h e t i t l e c o m p o u n d ( 40 m g , 0.08 mmol , 49 % ) w i t h  
29   t h e f o l l o w i n g c h a r a c t e r i s t i c s :

30

31   m.p. 215 - 216°C

32

33   A n a l y s i s c a l c u l a t e d f o r C<sub>23</sub>H<sub>31</sub>N<sub>3</sub>O<sub>6</sub>S<sub>2</sub>

1 Requires: C54.21 H6.13 N8.24

2 Found: C54.07 H6.19 N8.04

3

4  $\delta_H$  (250MHz,  $D_6$ -DMSO) 887 (1H, s, NH<sub>OH</sub>), 8.25 (1H,  
 5 d, J = 8.5 Hz, CONH), 8.09 (1H, d, J = 4.7 Hz,  
 6 thiophene-H), 7.83 (1H, m, CONHMe), 7.53 (1H, d, J = 3.  
 7 Hz, thiophene H), 7.25 - 7.12 (6H, m, phenyl and  
 8 thiophene-H), 4.36 (1H, m, CHCH<sub>2</sub>Ph), 3.38 (1H, dd, J =  
 9 14,11 Hz, SCH<sub>2</sub>), 2.87 (1H, dd, J = 14,5 Hz, CHCH<sub>2</sub>Ph),  
 10 2.75 (1H, dd, J = 14,10 Hz, CHCH<sub>2</sub>Ph), 2.70 - 2.36 (6H,  
 11 m, containing NHCH<sub>3</sub>), 1.20 (2H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub> and  
 12 CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.89 (1H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), and 0.75 (6H,  
 13 m, CH(CH<sub>3</sub>)<sub>2</sub>).

14

15  $\delta_C$  (63.9MHz,  $D_6$ -DMSO) 172.0, 171.2, 166.5, 140.0,  
 16 138.0, 135.4, 134.6, 129.0, 128.4, 128.2, 126.6, 54.3,  
 17 45.6, 37.5, 25.6, 25.0, 24.2, and 21.7.

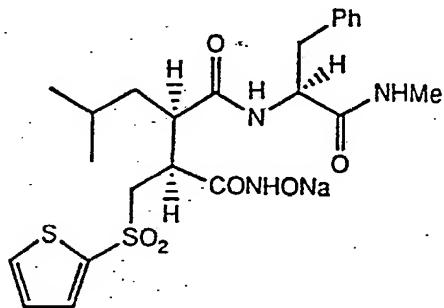
18

19 Example 24

20

21 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfonyl-  
 22 methylsuccinyl]-L-phenylalanine-N-methylamide sodium  
 23 salt.

24



25

26

27

28

29

30

31

32

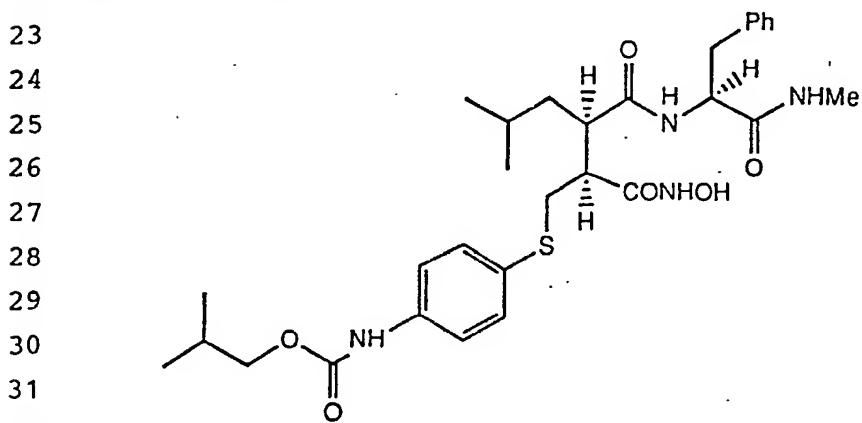
33 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfonyl-

1 methylsuccinyl]-L-phenylalanine-N-methylamide (50mg,  
2 0.1mmol) was dissolved in methanol (10ml) and sodium  
3 hydroxide solution (0.1M, 1.0ml) added to give a  
4 homogeneous solution. The methanol was removed under  
5 reduced pressure then the residual aqueous solution  
6 freeze dried to give the title compound (40mg).

7  
8  $\delta_{\text{H}}$  (250MHz, D<sub>6</sub>-DMSO) 8.66 (1H, s, NHOH), 8.25 (1H,  
9 d, J = 8.5 Hz, CONH), 7.83 (1H, m, CONHMe), 7.75 - 7.50  
10 (5H, m, aromatic H), 7.30 7.05 (5H, m, aromatic H),  
11 4.36 (1H, m, CHCH<sub>2</sub>Ph), 2.86 (1H, dd, J = 14,5 Hz,  
12 CHCH<sub>2</sub>Ph), 2.75 (1H, dd, J = 14,10 Hz, CHCH<sub>2</sub>Ph), 2.54  
13 (3H, d, J=4.5 Hz, NHCH<sub>3</sub>), 2.54 (2H, m), 1.30 (2H, m,  
14 CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub> and CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.86 (1H, m,  
15 CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.75 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and 0.71  
16 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

17  
18 Example 25

19  
20 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutyloxy-  
21 carbonylamino)phenyl)thiomethyl-succinyl]-L-phenyl-  
22 alanine-N-methylamide



1 methylsuccinyl]-L-phenylalanine-N-methylamide was  
2 prepared by the method described in example 1f to give  
3 a compound with the following characteristics.

4

5  $\delta_H$  (250MHz, D<sub>6</sub>-DMSO) 8.26 (1H, d, J = 8.5 Hz,  
6 CONH), 7.81 (1H, m, CONHMe), 7.27 - 7.15 (5H, m, phenyl  
7 H), 6.85 (2H, d, J = 8.5Hz, aromatic H), 6.46 (2H, d, J  
8 = 8.5Hz, aromatic H), 5.2 (1H, bs, CO<sub>2</sub>H), 4.48 (1H, m,  
9 CHCH<sub>2</sub>Ph), 2.90 (1H, dd, J = 13.5,4.3 Hz, CHCH<sub>2</sub>Ph), 2.75  
10 (1H, dd, J = 13.6, 10 Hz, CHCH<sub>2</sub>Ph), 2.56 (3H, d, J =  
11 4.5 Hz, NHCH<sub>3</sub>), 2.50 - 2.25 (3H, m), 2.03 (1H, d, J =  
12 10 Hz), 1.41 (1H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.26 (1H, m,  
13 CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.86 (1H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.75 (3H, d, J  
14 = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and 0.71 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>).  
15

16 b) N,N-Dimethylglycine (100mg, 0.97 mmol) was stirred  
17 in dry THF (50ml) and triethylamine (108mg, 1.1mmol)  
18 and isobutylchloroformate (146mg, 1.1mmol) were added.  
19 After 1h the product from example 26a (500mg, 1.1mmol)  
20 was added and the mixture stirred for a further 1h. The  
21 reaction was worked up by partitioning between citric  
22 acid and ethyl acetate, drying the organic layer and  
23 solvent removal to give the crude product (1g).  
24 Solution of the crude solid in ethyl acetate then  
25 precipitation with ether resulted in white crystals of  
26 the isobutylchloroformate derivative.

27

28 c) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutyloxy-  
29 carbonylamino) phenyl)thiomethyl-succinyl]-L-phenyl-  
30 alanine-N-methylamide

31

32 The product from example 26b was converted to the  
33 hydroxamic acid as described in example 1g. to give a  
compound with the following characteristics.

1 m.p. 198 - 200°C

2  
3  $[\alpha]_D = -8.5^\circ$  (c=1, methanol)

4  
5 Analysis calculated for  $C_{30}H_{42}N_4O_6S$

6 Requires: C61.41 H7.22 N9.55

7 Found: C62.04 H7.32 N9.67

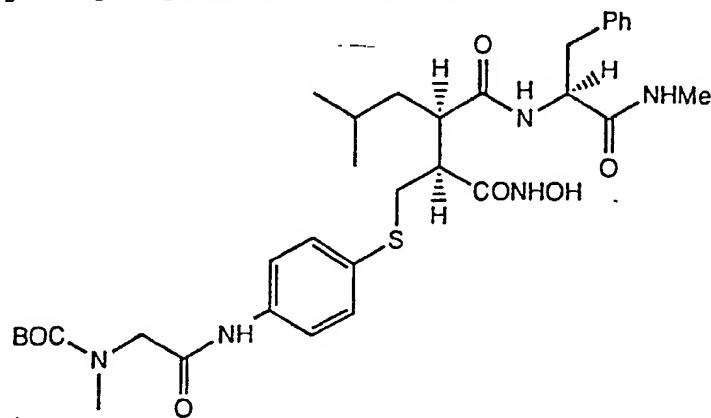
8  
9  $\delta_H$  (250MHz,  $D_6$ -DMSO) 9.60 (1H, s, NHOH), 8.83 (1H,  
10 s, NHOH), 8.31 (1H, d, J = 8.5 Hz, CONH), 7.85 (1H, m,  
11 CONHMe), 7.36 - 7.25 (4H, m, aromatic H), 7.14 - 7.05  
12 (3H, m, aromatic H), 6.91 (2H, d, J = 8.5Hz, aromatic  
13 H), 4.56 (1H, m, CHCH\_2Ph), 3.87 (2H, d, J = 7Hz,  
14 OCH2CH(CH\_3)\_2), 2.92 (1H, dd, J = 13.7, 4.0 Hz, CHCH\_2Ph),  
15 2.76 (1H, dd, J = 13.6, 10 Hz, CHCH\_2Ph), 2.58 (3H, d, J  
16 = 4.5 Hz, NHCH\_3), 2.50 - 2.34 (2H, m), 2.16 - 1.87 (3H,  
17 m), 1.35 (2H, m, CH2CH(CH\_3)\_2 and CH2CH(CH\_3)\_2), 0.93  
18 (6H, d, J = 6.6Hz, OCH2CH(CH\_3)\_2), 0.87 (1H, m,  
19 CH2CH(CH\_3)\_2), 0.75 (3H, d, J = 6Hz, CH(CH3)<sub>2</sub>), and  
20 0.71 (3H, d, J = 6Hz, CH(CH3)<sub>2</sub>).

21

22

23 Example 26

24  
25 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl-N-  
26 (tertbutoxycarbonyl)-glycylamino) phenyl)thiomethyl-  
27 succinyl]-Lphenylalanine-N-methylamide.



1    a) [4-Hydroxy-2R-isobutyl-3S-(4-(N-methyl-N-(tert-  
2    butoxycarbonyl)glycylamino) phenyl)thiomethyl-  
3    succinyl]-L-phenylalanine-N-methylamide was prepared as  
4    described in example 26b by substitution of N-BOC  
5    sarcosine for the acid component.

6  
7     $\delta_H$  (250MHz, D<sub>6</sub>-DMSO) 9.97 (1H, s, CO<sub>2</sub>H), 8.36 (1H,  
8    d, J = 8.5 Hz, CONH), 7.91 (1H, m, CONHMe), 7.48 (2H,  
9    d, J = 8.5Hz, aromatic H), 7.40 - 7.05 (5H, m, aromatic  
10   H), 6.97 (2H, d, J = 8.5Hz, aromatic H), 4.58 (1H, m,  
11   CHCH<sub>2</sub>Ph), 3.95 (2H, d, J = 9Hz, NCH<sub>2</sub>CO), 2.92 (4H, m+d,  
12   CHCH<sub>2</sub>Ph and BOCNCH<sub>3</sub>), 2.76 (1H, dd, J = 13,10 Hz,  
13   CHCH<sub>2</sub>Ph), 2.58 (3H, d, J = 4.5 Hz, NHCH<sub>3</sub>), 2.50 - 2.09  
14   (4H, m), 1.46 - 1.33 (11H, m + 2xs, (CH<sub>3</sub>)<sub>3</sub>C,  
15   CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub> and CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.87 (1H, m,  
16   CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.75 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and  
17   0.71 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

18  
19   b) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl- N-  
20   (tertbutoxycarbonyl)-glycylamino)phenyl)- thiomethyl-  
21   succinyl]-Lphenylalanine-N-methylamide was prepared  
22   from the material produced in example 27a as described  
23   in example 1g.

24  
25    $\delta_H$  (250MHz, D<sub>6</sub>-DMSO) 9.97 (1H, s, CONHOH), 8.83  
26   (1H, s, NH<sub>2</sub>O<sup>+</sup>), 8.32 (1H, d, J = 8.5 Hz, CONH), 7.86  
27   (1H, m, CONHMe), 7.46 (2H, d, J = 8.5Hz, aromatic H),  
28   7.28 - 7.00 (5H, m, aromatic H), 6.97 (2H, d, J =  
29   8.5Hz, aromatic H), 4.56 (1H, m, CHCH<sub>2</sub>Ph), 3.94 (2H, d,  
30   J = 9Hz, NCH<sub>2</sub>CO), 2.87 (4H, m+d, CHCH<sub>2</sub>Ph and BOCNCH<sub>3</sub>),  
31   2.76 (1H, m, CHCH<sub>2</sub>Ph), 2.57 (3H, d, J = 4.5 Hz, NHCH<sub>3</sub>),  
32   2.25 - 1.91 (2H, m), 1.42 - 1.30 (11H, m + 2xs,  
33   (CH<sub>3</sub>)<sub>3</sub>C, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub> and CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.92 (1H, m,  
CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.80 (3H, d, J = 6Hz, CH(CH<sub>3</sub>)<sub>2</sub>), and  
0.73 (3H, d, J=6Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

1  
2   Example 27  
3

4   Collagenase inhibition activity  
5

6   The potency of compounds of general formula I to act  
7   as inhibitors of collagenase (a metalloproteas  
8   involved in tissue degradation) was determined by the  
9   procedure of Cawston and Barrett, (Anal. Biochem., 99,  
10   340-345, 1979), hereby incorporated by reference,  
11   whereby a 1mM solution of the inhibitor being tested or  
12   dilutions thereof was incubated at 37° for 16 hours  
13   with collagen and collagenase (buffered with 25mM  
14   Hepes, pH 7.5 containing 5mM CaCl<sub>2</sub>, 0.05% Brij 35 and  
15   0.02% NaN<sub>3</sub>). The collagen was acetylated <sup>14</sup>C collagen  
16   prepared by the method of Cawston and Murphy (Methods  
17   in Enzymology, 80, 711, 1981), hereby incorporated by  
18   reference. The samples were centrifuged to sediment  
19   undigested collagen and an aliquot of the radioactive  
20   supernatant removed for assay on a scintillation  
21   counter as a measure of hydrolysis. The collagenase  
22   activity in the presence of 1 mM inhibitor, or a  
23   dilution thereof, was compared to activity in a control  
24   devoid of inhibitor and the results reported below as  
25   that inhibitor concentration effecting 50% inhibition  
26   of the collagenase (IC<sub>50</sub>).  
27

| 28 | <u>Compound of Example No.</u> | <u>IC<sub>50</sub></u> |
|----|--------------------------------|------------------------|
| 29 | 1                              | 20 nM                  |
| 30 | 2                              | 8 nM                   |
| 31 | 5                              | 3 nM                   |
|    | 6                              | (50% @ 1 mcM)          |

32  
33

1

2 Example 28

3

## 4 Stromelysin inhibition activity

5

6 The potency of compounds of general formula I to act as  
7 inhibitors of stromelysin was determined using the  
8 procedure of Cawston *et al* (Biochem. J., 195, 159-165  
9 1981), hereby incorporated by reference, whereby a 1mM  
10 solution of the inhibitor being tested or dilutions  
11 thereof was incubated at 37°C for 16 hours with  
12 stromelysin and  $^{14}\text{C}$  acetylate casein (buffered with  
13 25mM Hepes, pH 7.5 containing 5mM  $\text{CaCl}_2$ , 0.05% Brij 35  
14 and 0.02%  $\text{NaN}_3$ . The casein was  $^{14}\text{C}$  acetylated  
15 according to the method described in Cawston *et al*  
16 (Biochem. J., 195, 159-165, 1981), hereby incorporated  
17 by reference. The stromelysin activity in the presence  
18 of 1mM, or a dilution thereof, was compared to activity  
19 in a control devoid of inhibitor and the results  
20 reported below as that inhibitor concentration  
21 effecting 50% inhibition of the stromelysin ( $\text{IC}_{50}$ ).  
22

23

Compound of Example No. $\text{IC}_{50}$ 

24

1

10 nM

25

2

20 nM

26

27 Examples of unit dosage compositions are as follows:  
28  
29  
30  
31  
32  
33

1

2

3

4 Example 29

5

6 **Capsules:**

|    |                      | Per 10,000         |
|----|----------------------|--------------------|
|    | <u>Ingredients</u>   | <u>Per Capsule</u> |
|    |                      | <u>Capsules</u>    |
| 10 | 1. Active ingredient |                    |
| 11 | Cpd. of Form. I      | 40.0 mg            |
| 12 | 2. Lactose           | 150.0 mg           |
| 13 | 3. Magnesium         |                    |
| 14 | stearate             | <u>4.0 mg</u>      |
| 15 |                      | <u>40 g</u>        |
|    |                      | 194.0 mg           |
|    |                      | 1940 g             |

16

17 **Procedure for capsules:**

18

19 Step 1. Blend ingredients No. 1 and No. 2 in a  
20 suitable blender.21 Step 2. Pass blend from Step 1 through a No. 30 mesh  
22 (0.59 mm) screen.23 Step 3. Place screened blend from Step 2 in a  
24 suitable blender with ingredient No. 3 and  
25 blend until the mixture is lubricated.26 Step 4. Fill into No. 1 hard gelatin capsule shells  
27 on a capsule machine.

28

29

30

31

32

33

1    Example 30

2

3        Tablets:

| 4  |                      |                   | Per 10,000     |
|----|----------------------|-------------------|----------------|
| 5  | <u>Ingredients</u>   | <u>Per Tablet</u> | <u>Tablets</u> |
| 6  |                      |                   |                |
| 7  | 1. Active ingredient |                   |                |
| 8  | Cpd. of Form. I      | 40.0 mg           | 400 g          |
| 9  | 2. Corn Starch       | 20.0 mg           | 200 g          |
| 10 | 3. Alginic acid      | 20.0 mg           | 200 g          |
| 11 | 4. Sodium alginate   | 20.0 mg           | 200 g          |
| 12 | 5. Magnesium         |                   |                |
| 13 | stearate             | <u>1.3 mg</u>     | <u>13 g</u>    |
| 14 |                      | 101.3 mg          | 1013 g         |

15

## 16      Procedure for tablets:

17      Step 1. Blend ingredients No. 1, No. 2, No. 3 and No.  
18                  4 in a suitable mixer/blender.

19      Step 2. Add sufficient water portionwise to the blend  
20                  from Step 1 with careful mixing after each  
21                  addition. Such additions of water and mixing  
22                  until the mass is of a consistency to permit  
23                  its conversion to wet granules.

24      Step 3. The wet mass is converted to granules by  
25                  passing it through an oscillating granulator  
26                  using a No. 8 mesh (2.38) screen.

27      Step 4. The wet granules are then dried in an oven at  
28                  140°F (60°C) until dry.

29      Step 5. The dry granules are lubricated with  
30                  ingredient No. 5.

31      Step 6. The lubricated granules are compressed on a  
32                  suitable tablet press.

33

1    Example 31

2

3    **Intramuscular Injection:**

| 4 | <u>Ingredient</u>        | <u>Per ml.</u> | <u>Per liter</u> |
|---|--------------------------|----------------|------------------|
| 5 | 1. Compound of Formula I |                |                  |
| 6 | Active ingredient        | 10.0 mg        | 10 g             |
| 7 | 2. Istonic buffer        |                |                  |
| 8 | solution pH 4.0.         | q.s.           | q.s.             |

9

10    **Procedure:**

- 11    Step 1. Dissolve the active ingredient in the buffer  
12    solution.
- 13    Step 2. Aseptically filter the solution from Step 1.
- 14    Step 3. The sterile solution is now aseptically  
15    filled into sterile ampoules.
- 16    Step 4. The ampoules are sealed under aspetic  
17    conditions.

18

19    Example 32

20

21    **Suppositories:**

| 22 |                        |                  | <u>Per</u>        |
|----|------------------------|------------------|-------------------|
| 23 | <u>Ingredients</u>     | <u>Per Supp.</u> | <u>1,000 Supp</u> |
| 24 | 1. Compound of Form. I |                  |                   |
| 25 | Active ingredient      | 40.0 mg          | 40 g              |
| 26 | 2. Polyethylene Glycol |                  |                   |
| 27 | 1000                   | 1350.0 mg        | 1,350 g           |
| 28 | 3. Polyethylene Glycol |                  |                   |
| 29 | 4000                   | 450.0 mg         | 450 g             |
| 30 |                        | 1840.0 mg        | 1,840 g           |

31

32

33

- 1      Procedure:
- 2      Step 1.   Melt ingredient No. 2 and No. 3 together and  
3               stir until uniform.
- 4      Step 2.   Dissolve ingredient No. 1 in the molten mass  
5               from Step 1 and stir until uniform.
- 6      Step 3.   Pour the molten mass from Step 2 into  
7               suppository moulds and chill.
- 8      Step 4.   Remove the suppositories from moulds and  
9               wrap.

10

11      Example 33

12

## 13      Eye Ointment

14

15      An appropriate amount of a compound of general formula  
16      I is formulated into an eye ointment base having the  
17      following composition:

18

|    |                      |     |
|----|----------------------|-----|
| 19 | Liquid paraffin      | 10% |
| 20 | Wool fat             | 10% |
| 21 | Yellow soft paraffin | 80% |

22

23      Example 34

24

## 25      Topical skin ointment.

26

27      An appropriate amount of a compound of general formula  
28      I is formulated into a topical skin ointment base  
29      having the following composition:

30

|    |                     |     |
|----|---------------------|-----|
| 31 | Emulsifying wax     | 30% |
| 32 | White soft paraffin | 50% |
| 33 | Liquid paraffin     | 20% |

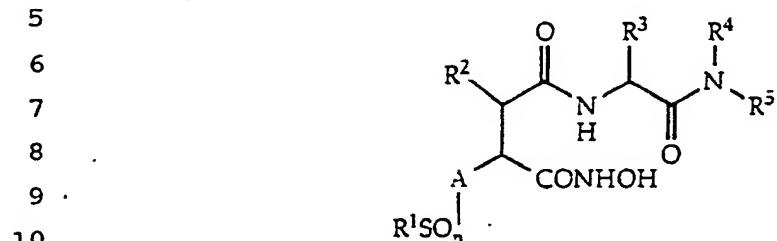
1      CLAIMS

2

3      1. A compound of general formula I:

4

5



(I)

10

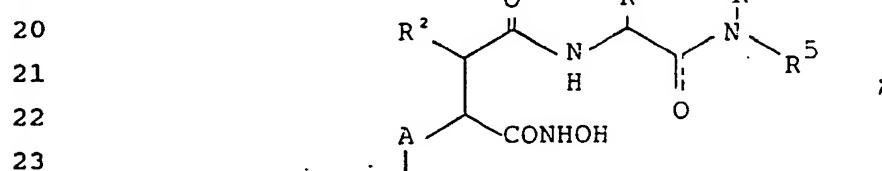
11    wherein:

12

13    R<sup>1</sup> represents a C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, thiophenyl,  
 14    substituted phenyl, phenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 15    heterocyclyl, (C<sub>1</sub>-C<sub>6</sub>)alkylcarbonyl or phenacyl or  
 16    substituted phenacyl group; or when n = 0, R<sup>1</sup>  
 17    represents SR<sup>X</sup>, wherein R<sup>X</sup> represents a group:

18

19



22

23

24

25

26    R<sup>2</sup> represents a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
 27    alkenyl, phenyl (C<sub>1</sub>-C<sub>6</sub>) alkyl,  
 28    cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl or cycloalkenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl  
 29    group;

30

31

32    R<sup>3</sup> represents an amino acid side chain or a C<sub>1</sub>-C<sub>6</sub>  
 33    alkyl, benzyl, (C<sub>1</sub>-C<sub>6</sub> alkoxy)benzyl or  
 benzyl oxy(C<sub>1</sub>-C<sub>6</sub> alkyl) or benzyl oxy benzyl group;

1      R<sup>4</sup>    represents a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl group;

2

3      R<sup>5</sup>    represents a hydrogen atom or a methyl group;

4

5      n    is an integer having the value 0, 1 or 2; and

6

7      A    represents a C<sub>1</sub>-C<sub>6</sub> hydrocarbon chain, optionally  
8      substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl  
9      or substituted phenyl groups;

10

11     or a salt thereof.

12

13     2. A compound as claimed in Claim 1, in which the  
14      chiral centre adjacent the substituent R<sup>3</sup> has S  
15      stereochemistry.

16

17     3. A compound as claimed in Claim 1 or 2, wherein the  
18      chiral centre adjacent the substituent R<sup>2</sup> has R  
19      stereochemistry.

20

21     4. A compound as claimed in Claim 1, 2 or 3, in which  
22      R<sup>1</sup> represents a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl,  
23      thiophenyl, benzyl, acetyl or phenacyl group.

24

25     5. A compound as claimed in any one of Claims 1 to 4,  
26      wherein R<sup>2</sup> represents a C<sub>3</sub>-C<sub>6</sub> alkyl group.

27

28     6. A compound as claimed in any one of Claims 1 to 5,  
29      wherein R<sup>3</sup> represents a benzyl or  
30      4-(C<sub>1</sub>-C<sub>6</sub>)alkoxyphenylmethyl or benzyloxybenzyl group.

31

32     7. A compound as claimed in any one of Claims 1 to 6,  
33      wherein R<sup>4</sup> represents a C<sub>1</sub>-C<sub>4</sub> alkyl group.

1    8. A compound as claimed in any one of Claims 1 to 7,  
2    wherein R<sup>5</sup> represents a hydrogen atom.

3  
4    9. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthio-  
5    methyl)-succinyl]-L-phenylalanine-N-methylamide,

6  
7    [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthio-  
8    methyl) succinyl]-L-phenylalanine-N-methylamide,

9  
10   [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzylthiomethyl)  
11   succinyl]-L-phenylalanine-N-methylamide,

12  
13   [4-(N-Hydroxyamino)-2R-isobutyl-3S-(acetylthiomethyl)  
14   succinyl]-L-phenylalanine-N-methylamide or

15  
16   [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiolmethyl)  
17   succinyl]-L-phenylalanine-N-methylamide

18  
19   [4-(N-Hydroxyamino)-2R-isobutyl-3S-(pivaloylthiomethyl)  
20   succinyl]-L-phenylalanine-N-methylamide

21  
22   [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)  
23   succinyl]-L-phenylalanine-N-methylamide sodium salt

24  
25   [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenyl-  
26   thiomethyl)succinyl]-L-phenylalanine-N-methylamide

27  
28   [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-  
29   thiomethyl)succinyl]-L-phenylalanine-N-methylamide

30  
31   [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thiophenethio-  
32   methyl)succinyl]-L-phenylalanine-N-methylamide sodium  
33   salt

- 1 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenyl-thiomethyl)succinyl]-L-phenylalanine-N-methylamide
- 2 sodium salt
- 3
- 4
- 5 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-tertbutylphenyl-thiomethyl)succinyl]-L-phenylalanine-N-methylamide
- 6
- 7
- 8 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2,4-dimethylphenyl-thiomethyl) succinyl]-L-phenylalanine-N-methylamide
- 9
- 10
- 11 bis-S,S'-{[4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiomethyl)succinyl]-L-phenylalanine-N-methylamide} disulphide
- 12
- 13
- 14 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-bromophenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide
- 15
- 16
- 17 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-chlorophenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide
- 18
- 19
- 20 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-methylphenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide
- 21
- 22
- 23 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-amino-phenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide
- 24
- 25
- 26
- 27 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphinyl-methylsuccinyl]-L-phenylalanine-N-methylamide
- 28
- 29
- 30 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphonyl-methylsuccinyl]-L-phenylalanine-N-methylamide
- 31
- 32
- 33

- 1 [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylsulphiny1-  
2 methylsuccinyl]-L-phenylalanine-N-methylamide
- 3
- 4 [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylsulphonyl-  
5 methylsuccinyl]-L-phenylalanine-N-methylamide
- 6
- 7 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphonyl-  
8 methylsuccinyl]-L-phenylalanine-N-methylamide sodium  
9 salt
- 10
- 11 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutoxycarbonylamino)phenyl)thiomethylsuccinyl]-L-phenyl-  
12 alanine-N-methylamide
- 13
- 14 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl-N-(tert-butoxycarbonyl)-glycylamino)phenyl)thiomethyl-  
15 succinyl]-L-phenylalanine-N-methylamide
- 16
- 17 or, where appropriate, a salt of such a compound.
- 18
- 19
- 20 10. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide, or
- 21
- 22
- 23
- 24 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiomethylsuccinyl]-L-phenylalanine-N-methylamide
- 25
- 26
- 27 or a salt thereof.
- 28
- 29 11. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide or a  
30 salt thereof.
- 31
- 32
- 33

1    12. A compound as claimed in any one of claims 1 to 11  
 2    for use in human or veterinary medicine.

3

4    13. The use of a compound as claimed in any one of  
 5    claims 1 to 11 in the preparation of an agent for use  
 6    in the management of disease involving tissue  
 7    degradation and/or in the promotion of wound healing.

8

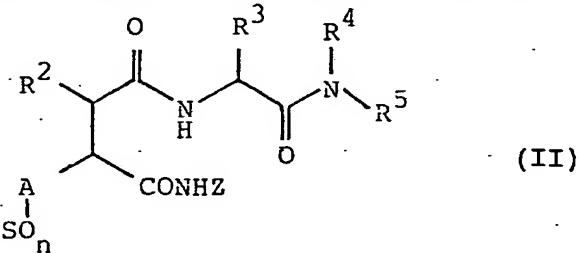
9    14. A pharmaceutical or veterinary formulation  
 10 comprising a compound as claimed in any one of claims 1  
 11 to 11 and a pharmaceutically and/or veterinarily  
 12 acceptable carrier.

13

14    15. A process for preparing a compound of general  
 15 formula I as defined in claim 1, the process  
 16 comprising:

17

18    (a) deprotecting a compound of general formula II



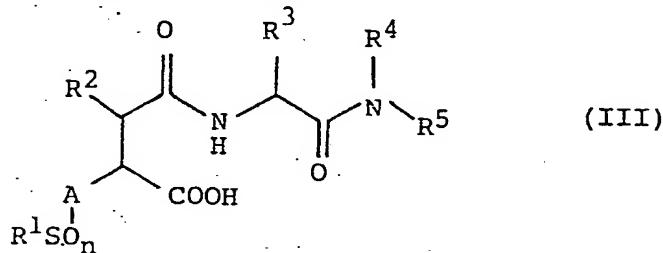
24    wherein:  $\text{R}^1 \text{SO}_n$

25

26     $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{A}$  and  $n$  are as defined in  
 27 general formula I and  $\text{Bn}$  represents a  
 28 benzyloxycarbonyl group; or

29

30    (b) reacting a compound of general formula III



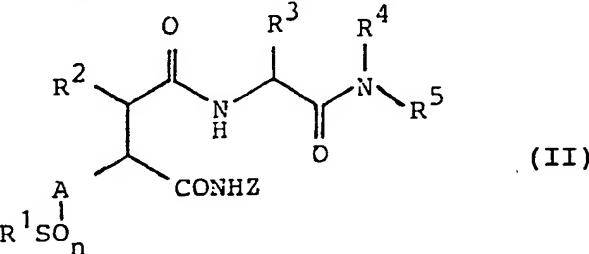
1 wherein:

2           R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, A and n are as defined in  
3           general formula I,

4           with hydroxylamine or a salt thereof; and  
5

6           (c) optionally after step (a) or step (b) converting a  
7           compound of general formula I into another compound of  
8           general formula I.

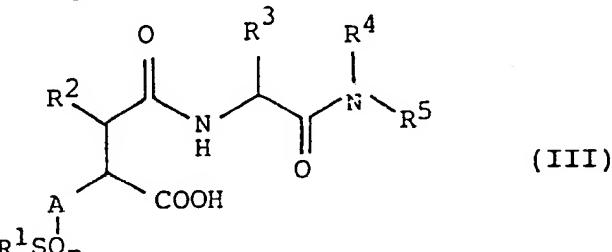
9           16. A compound of general formula II



10          wherein:

11          R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, A and n are as defined in  
12          general formula I and Z represents a protecting  
13          group.

14          17. A compound of general formula III



15          wherein:

16          R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, A and n are as defined in  
17          general formula I.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 89/01399

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) \*

According to International Patent Classification (IPC) or to both National Classification and IPC  
 IPC<sup>5</sup> C 07 C 323/62, 323/60, C 07 D 333/34, C 07 C 327/32,  
 IPC: 317/50, 313/48, A 61 K 31/13, 31/38

## II. FIELDS SEARCHED

Minimum Documentation Searched ?

| Classification System                                                                                                              | Classification Symbols                                                 |
|------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| IPC <sup>5</sup>                                                                                                                   | C 07 C 259/00, 323/00, C 07 D 333/00,<br>C 07 C 327/00, 317/00, 313/00 |
| Documentation Searched other than Minimum Documentation<br>to the Extent that such Documents are Included in the Fields Searched * |                                                                        |

## III. DOCUMENTS CONSIDERED TO BE RELEVANT \*

| Category * | Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>               | ! Relevant to Claim No. <sup>13</sup> |
|------------|------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| A          | EP, A, 0236872 (F. HOFFMANN-LA ROCHE)<br>16 September 1987<br>see claim 1<br>cited in the application<br>--                  | 1-17                                  |
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\* Special categories of cited documents: <sup>10</sup>

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

8th March 1990

Date of Mailing of this International Search Report

17 APR. 1990

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

  
MISS T. TAZELAAR

**III. DOCUMENTS CONSIDERED TO BE RELEVANT : (CONTINUED FROM THE SECOND SHEET)**

| Category * | Citation of Document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                  | Relevant to Claim No |
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 8901399  
SA 33118

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 04/04/90. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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